Medical Grand Rounds

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IMMUNIZATION IN INTERNAL MEDICINE

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OUTLINE

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INTRODUCTION

Primarily once considered the province of the pediatrician or the family physician, changes in disease patterns, new vaccines and the emergence of foreign travel as a common event, have made it increasingly important for the internist to be knowledgable about immunization and its role in the practice of internal medicine.

CASE REPORT

To the best of her knowledge, the patient, a 73 year old woman, had received only one "tetanus shot" 20 years prior to her present illness. On November 11, 1977, she received a wound to the left lower extremity. Five days later, her personal physician saw her for the wound, removed a wooden splinter and administered a dose of adsorbed tetanus toxoid intramuscularly. Three days after this, she developed trismus and difficulty swallowing. She was hospitalized and an ENT specialist determined that there was no local cause for the trismus. She was subsequently transferred to Parkland Memorial Hospital and placed in the Medical Intensive Care Unit. Physical examination on admission revealed slight nuchal rigidity, trismus, abdominal muscle tenseness, hyper-reflexia of the left lower extremity and unsustained ankle clonus. The next day, the patient could not open her jaw at all, the neck was increasingly stiff and the left leg was completely rigid. An elective tracheostomy was performed. Subsequently, she developed typical tetanic spasms which were managed with diazepam therapy. Therapy for the tetanus included tetanus hyper-immune globulin, 5000 units intramuscularly, intravenous penicillin and thorough debridement of the wound. She was given a dose of adsorbed tetanus toxoid and another dose subsequently in one month. The third dose of tetanus toxoid is scheduled to be given approximately one year after the second dose. The total length of the hospitalization extended from November 27, 1977 to January 6, 1978. The tracheostomy was removed on December 31, 1977, after which time the patient was transferred to the open ward. Total cost for the hospitalization exclusive of physicians' charges was $16,500.

CASE REPORT

A 26 year old male medical student from Southwestern Medical School was performing an elective clerkship in infectious diseases at a military base in San Antonio. While there, he was exposed to numerous military recruits with the measles (rubeola). Previously in excellent health, he then developed "flu-like" symptoms over a period of 5 days characterized by an objective fever to 102°, malaise, mild conjunctivitis bilaterally, and an increasingly severe dry, hacking cough. Four days into the illness, he noted erythematous, granular lesions appearing predominately on the buccal mucosa. The following day an erythematous, non-pruritic, maculo-papular rash appeared over the face and then during the following 10 days progressed in a symmetrical fashion down the entire body. The rash became confluent over the face, arms, shoulders and upper trunk. Throughout the course of the illness, a severe cough was prominent along with spiking temperatures to 104.6°, during which time the patient was somewhat delirious. Ten to eleven days following the onset of the prodrome, the rash began to resolve and the patient began to improve. He returned to work 3 weeks following the onset of his illness without sequelae. The patient had never been vaccinated against rubeola but remembered having been told that he had the disease when he was five years old.

CASE REPORT

Following a month's illness characterized by fever and weight loss, this 34 year old man was found to have Hodgkin's disease, lymphocyte depletion type. He underwent staging laporotomy with splenectomy. The liver biopsies were negative for the presence of Hodgkin's disease but a bone marrow examination was positive. He was classified as Stage IVB and treated with 6 courses of Bleo-MOPP. During one of the courses of treatment in March, 1977, he developed an episode of pneumococcal pneumonia. In May, 1977 he had another episode of pneumococcal pneumonia with the development of a murmur and multiple positive blood cultures. He was then treated for a month for a presumptive diagnosis of pneumococcal endocarditis. He subsequently moved to Dallas where he was followed in the Hematology Clinic. In March, 1978 he developed pneumococcal pneumonia again for which he was successfully treated at Parkland Memorial Hospital. On April 13, 1978 he developed a headache and fever and was hospitalized at Parkland. On admission, he had a temperature of 106° with nuchal rigidity. He rapidly became delirious and combative. A lumbar puncture revealed 463 WBC's with 81% PMN's. The cerebrospinal fluid culture grew a heavy growth of Pneumococcus as did three blood cultures. He was started on penicillin almost immediately upon entrance into Parkland Hospital. Despite early therapy, he died on April 17. The pneumococcus was found to be sensitive to penicillin with a MIC less than 0.125 units/ml.

THE HISTORY OF IMMUNIZATION

The history of immunization begins with Edward Jenner and his epochal investigations documenting the prevention of smallpox by the prior inoculation of the virus of cowpox and extends to the present where smallpox has all but been eliminated from the world [Table 1]. At the time of the publication of Jenner's work, smallpox accounted for 10-20% of all deaths occurring in the United Kingdom. No further vaccines were developed until the beginning of the "Golden Age" of bacteriology (1876) when, in the course of a decade, enormous strides were made in the microbiological elucidation of the causes of disease. There was intense competition between the "Berlin school" led by Robert Koch and the "Paris school" headed by Louis Pasteur. The development of the world's second vaccine, directed against fowl cholera, was made by serendipity when it was shown that the prior inoculation of an aged culture of the microorganism protected against subsequent challenge by the virulent bacillus. Later, in 1885, Pasteur developed a live rabies vaccine attenuated by drying and which led to the prophylactic treatment of rabies. Interestingly, although Pasteur's experiments were scientifically based, he had no concept of immunity, believing that the attentuated agents were utilizing essential nutritional substances that no longer were available for the virulent microorganism. It remained for Behring, Ehrlich and Metchnikoff to formulate our beginning ideas concerning immunity.

The most successful bacterial vaccines were directed against the toxins of diphtheria and tetanus. In the beginning, however, the diphtheria vaccine consisted of a mixture of toxin and antitoxin (toxin-antitoxin mixture, TAM: toxin-antitoxin floccules, TAF). In actual usage, instances resulted

where the toxin was not counter-balanced by a corresponding amount of antitoxin and several significant accidents occurred. With the successful modification of toxin by formalin, toxoid preparations became available and are the basis of our current vaccines. The addition of adjuvants (alum-precipitation) improved the immunogenicity of the toxoids. The other bacterial vaccines directed against typhoid-paratyphoid, cholera and plague were actually crude preparations of whole, dead organisms. They remain relatively poor immunogens whose efficacy in controlled field trials was not proven until the 1960's. The major important modern thrust in the development of bacterial vaccines depends on the isolation, characterization and purification of the specific antigens responsible for virulence and immunity. Examples of such antigens include the toxin elaborated by *Cholera vibrio* and the polysaccharide capsular material from Groups A and C meningococci and the pneumococcus.

The viral vaccines received an important impetus when it was learned that some viruses could be grown in embryonated chicken eggs and later in tissue culture. The most successful viral vaccines today are living, attenuated viruses which apparently give long-term immunity with a single injection with relatively few side effects. Inactivated vaccines exist for influenza, rabies and poliomyelitis. Inactivated viral vaccines against rubeola and respiratory syncytial virus were removed from use and development when it was learned that an altered, sometimes more severe disease state could be produced after natural challenge with the wild-type virus in patients immunized with the inactivated vaccines. A major thrust in the development of new viral vaccines or the improvement of older ones is to

insure the safety and purity of the cell substrate on which the viruses are grown by using stocks of carefully bred animals (dogs, ducks, chickens) or human cell strains which have been carefully studied for safety and which theoretically could yield an almost infinite supply of cells (WI-38).

Paradoxically, modern developments in the preparation of vaccines are sometimes thwarted by the fact that the more purified vaccines may be less immunogenic. At the present time, development of new vaccines against agents such as *Hemophilus influenzae*, the Group B streptococcus and even *Neisseria gonorrhoae* now seem ultimately possible. Limitations as to their utility include precise demonstration of their threat as diseases to the health of the population and to the extent that the population at large will accept these new antigens as a part of health prevention maintenance.

TABLE 1

YEAR	MAJOR PERSONS INVOLVED	EVENT
1798	Jenner	Smallpox vaccination
1876	Koch	Anthrax bacillus discovered. The "Golden Age" of bacteriology begins.
1880	Pasteur	Fowl cholera vaccine
1885	Pasteur	Rabies vaccine
1891	Behring and Kitasato	Diphtheria and tetanus antitoxins
1897	Ehrlich	Standardization of diphtheria antitoxin
1898	Wright	Typhoid vaccine
1913	Behring	Toxin-antitoxin mixtures for human immunization against diphtheria
1921	Calmette and Guerin	B.C.G. vaccine for tuberculosis
1923	Ramon	Diphtheria toxoid for human immunization
1927	Ramon and Zoeller	Tetanus toxoid for human immunization
1931	Glenny and Barr	Diphtheria alum-precipitated toxoid
1933-1936	Sauer; Kendrick	Pertussis vaccine
1936	Theiler, Sawyer and Sellards	17 D yellow fever vaccine
1937	Francis	Influenza virus vaccines
1949	Enders, Robbins and Weller	Cultivation of poliomyelitis virus in tissue culture
1954	Salk	Inactivated poliomyelitis vaccine tested in field trial

TABLE 1 Cont'd

YEAR	MAJOR PERSON INVOLVED	EVENT
1957	Sabin	Oral poliomyelitis vaccine
1963	Enders	Attentuated rubeola vaccine
1967	Parkman and Meyer	Attentuated rubella vaccine
1969	Hilleman	Attentuated mumps vaccine
1969	Gotschlich, Goldschneider and Artenstein	Meningococcal polysaccharide vaccines (Groups A and C)
1978	Austrian	Licensure of pneumococcal polysaccharide vaccine

ACCIDENTS ASSOCIATED WITH IMMUNIZATION

Since the beginning of immunization, there have always been accidents associated with either the faulty production or the administration of the vaccine. In terms of the fault in production, the defect might lie in 1) the fact that the vaccine virus or toxin was incompletely inactivated, 2) that a foreign toxin was present, 3) that a wrong culture was utilized, or 4) that there was either bacterial or viral contamination. Improper administration of the vaccine might occur because a non-sterile apparatus was used or that bacterial contamination was introduced by operator error. Accidents, usually occurring in the early phases of specific vaccine manufacture, were relatively common during the first part of this century when vaccines were made in small laboratories under essentially no form of quality control. Accidents must be considered separately from the complications that might ensue after immunization. Complications result from the inherent toxicity of the product. We will consider three accidents associated with immunization in detail. Elucidation of the causation of these accidents led to improvements in vaccine manufacture because they pointed to that part of the manufacturing cycle most vulnerable to error.

Administration of toxin-antitoxin mixture (TAM) in Dallas, Texas, 1919. The earliest applied form of immunization against diphtheria consisted of injecting toxin that had been neutralized by equine antitoxin. In retrospect, it seems easy to imagine how error could result from manufacture of such a complicated product. On October 23, 1919, the municipal hospital, private practitioners and public health personnel began administering TAM to the children of the city (Dallas). After multiple injections had been given, a subgroup of

children who had been immunized on November 12 and 13 began to have severe reactions which could all be traced to the use of a particular batch of TAM prepared by one manufacturer. It cannot now be ascertained how many total children were injected by the toxic batch but 120 children were later specifically investigated. Of the 120 children, 24 suffered no reaction; they were presumed to have been immune. Ninety-six children had local and systemic reactions. Among the 96 reactions, 10 were very severe and resulted in death, 74 were severe, and 12 were moderate. Seven of the 10 children who died succumbed within 2 weeks; the other 3 died 31, 39 and 46 days after the injection from myocarditis and paralysis of the muscles of respiration. It was found that the implicated lot of vaccine had 50 times the permissible quantity of toxin. The clinical picture in the affected children consisted of a severe local reaction with erythema and edema progressing to vesicle formation and eventually denudation of an area of skin that might be 6-12 square inches in size. Myocarditis appeared on the 9th or 10th day after injection. Partial paralysis of one or more muscle groups occurred in all patients. Interestingly, the first muscles affected were the muscles of the eye followed, in order, by palatal paralysis and then the muscles of respiration. In a similar accident in Medellin, Columbia in 1930, it was noted that after peripheral inoculation of the toxin, a false membrane was observed over the tonsils in many of the children. This observation was of particular interest, because, in a natural experiment it appeared as if the diphtheria toxin had a special affinity for the pharyngeal mucosa and that the local multiplication of diphtheria bacilli was not necessary for membrane formation provided toxin was present.

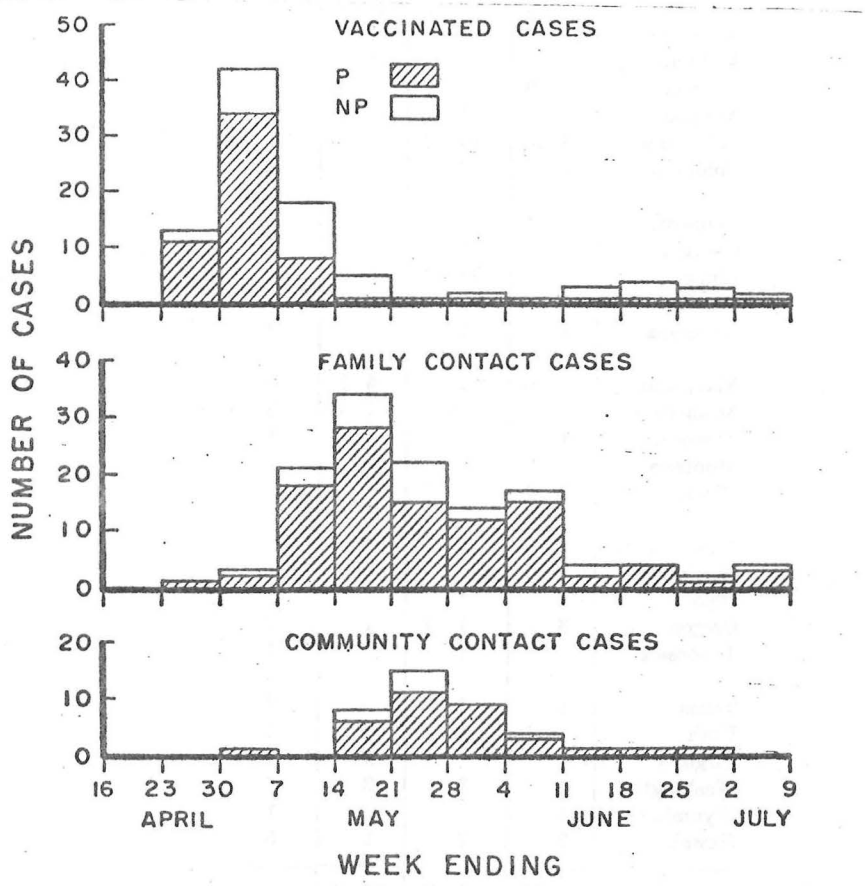
With the advent of formalin treatment of toxin to produce toxoid, mixtures of toxin and antitoxin in immunogens could be abandoned and such disasters as that occurring in Dallas never repeated. Presently, the pediatric and adult doses of diphtheria toxoid are among the safest vaccines available. The accident in Dallas was an accompaniment of the complexity of the vaccine manufacturing process. It did give rise to anti-vaccination sentiment which was eventually dispelled by the advent of a safer vaccine and the disappearance of diphtheria from populations which had been immunized.

Hepatitis after yellow fever vaccination, 1942. At a press conference in Washington on July 24, 1942, the Secretary of War reported that 28,585 cases of jaundice had been observed in the Army between January 1 and July 4 after yellow fever vaccination, and of these 62 had proved fatal. Death, when it occurred, was usually 2-6 weeks after the onset of illness. The conclusion was reached that the agent was present in the normal human serum which had been used as a stabilizing agent in the preparation of the vaccine. After serum was omitted from the vaccine, cases ceased to occur. The incubation period was protracted and it is now known that the transmissible agent was hepatitis B virus.

The Cutter incident. After the successful attempt of Enders, Weller and Robbins to cultivate poliomyelitis virus in tissue culture, Salk introduced a vaccine containing the three polymyelitis virus types which had been inactivated by formalin. The Francis Field Trial then followed which indicated that the vaccine had a protective effect. Six different pharmaceutical manufacturers were then licensed to produce the vaccine which was then

distributed to approximately 5 million persons, beginning in April, 1955. On April 26, 6 cases of poliomyelitis were recognized in children who had received the Cutter vaccine. The cases had a short incubation period following receipt of the vaccine (median of 9 days) [Figure 1]. That part of the body showing paralysis first was often the arm into which the vaccine had been injected. This feature is characteristic of inoculation poliomyelitis. Cases then occurred in family and community contacts. The original cases were examined for fecal excretion of the virus and 80% of the injected children experiencing paralysis had poliomyelitis virus, type 1 isolated from stool. The virus was also actually recovered from lots of the implicated vaccine. As soon as the early cases appeared, all lots of the Cutter vaccine were removed from use. Altogether in the epidemic there were 260 cases of poliomyelitis scattered throughout the country of which 10 proved to be fatal [Table 2]. There were 94 cases in vaccinated persons, 126 cases in family contacts and 40 cases in community contacts. Inquiry showed that in the preparation of the vaccine the virus in some lots had not been inactivated by treatment with formalin. The Cutter incident led to growing awareness of the necessity of adequate quality control in the preparation of vaccines. It also illustrated the necessity of surveillance to detect unforeseen incidents. Projected into the setting of the times, early withdrawal of lots of the vaccine in the midst of a nationwide effort to prevent the coming summer's cases of poliomyelitis, was an insightful and courageous decision which undoubtedly prevented additional cases of the disease.

Figure 1



Cutter-associated cases by onset

Amer. J. Hyg. 78:41, 1963

Table 2

*Poliomyelitis cases associated with Cutter vaccine**

State	Vaccinated cases		Family contact cases		Community contact cases		Totals
	P	NP	P	NP	P	NP	
Alabama					1		1
Arizona		2		3			5
Arkansas			1			1	2
California	23	22	40	9	3	2	99
Colorado	1		2				3
Connecticut		1					1
Georgia	1		3				4
Idaho	18	7	34	7	18	2	86
Illinois	1						1
Louisiana	1		1				2
Maryland			1		4	1	6
Minnesota					1	1	2
Missouri	1						1
Montana			1				1
Nevada	3	1	4	1			9
New Mexico	1	1	4	3			9
New York		1					1
Ohio	1		1				2
Oregon	3		1	2	1		7
Tennessee			1				1
Texas	1		1				2
Utah			1				1
Virginia					1		1
Washington	1		3		2	1	7
Wyoming	1						1
Hawaii	2		2		1		5
Totals	59	35	101	25	32	8	
	94		126		40		260

* Includes all cases in study. All onsets April 17 through June 30.

Am. J. Hyg. 78:39, 1963

THE COMPLICATIONS OF IMMUNIZATION

As stated by Sir Graham S. Wilson in "The Hazards of Immunization", "there can be no insurance without a premium". Each vaccine being a biological product has an inherent toxicity which must be weighed against the value of protection against disease afforded by the vaccine. Complications may be local and related to a product like endotoxin which is an inherent part of killed vaccines against Gram negative bacilli. The Arthus phenomenon may be involved in the pathogenesis of some of the local reactions. Sterile abscesses may occur after inoculation. In part, the severity of the local reaction may be lessened by further purification of the product. However, vaccination against typhoid fever, for example, must be accompanied by side-effects since the product producing the reaction, viz., endotoxin, is an inherent part of the vaccine itself. Influenza vaccine has been substantially freed from contaminating egg products by the process of zonal ultracentrifugation. Part of the side-reactions, both of a local and systemic nature, however, are related to the virus itself. If the virus is chemically split to produce a sub-unit vaccine, the side-effects are lessened but the vaccine is a less effective immunogen, especially when administered to younger persons who have had no prior immunological experience with any of the influenza viruses. Febrile reactions with malaise and myalgias following immunization pathogenetically are caused by those mechanisms involved in the genesis of the local reaction. Severe allergic reactions may complicate immunization and may include some or all of the classic manifestations of anaphylaxis. Since

many vaccines are produced in embryonated chicken eggs, persons with allergies to egg products should be advised not to be immunized or to be immunized only with appropriate precautions.

The side-reactions following smallpox immunization were often severe and prompted a reconsideration of our vaccination policies at a time when smallpox was still endemic in the world. These side-reactions essentially preclude the use of this vaccine for any purpose other than that originally intended. Use of the smallpox vaccine to attempt to alter recurrent herpetic infections or to cure warts has no scientific documentation and may be accompanied by serious consequences. The skin reactions following smallpox vaccination have been investigated in detail and consisted of effects due to the replication of the virus and allergic manifestations. The virus replicating in the typical Jennerian vesicle could be transferred by inoculation onto other parts of the body, including the eye. It could also be transmitted to close contacts of the recipient of the vaccine. The virus might become generalized by viremia and affect all areas of the skin or might be concentrated in specific areas as in eczema vaccinatum. In certain immune-deficient individuals, the virus inexorably and slowly spread from the primary focus of vaccination. This latter reaction, vacinnia necrosum, was invariably fatal prior to the advent of vaccinia immune globulin and the thiosemicarbazones. Allergic reactions consisted of urticaria, toxic erythema, anaphylactoid purpura (leukocytoclastic vasculitis) and generalized erythema multiforme.

In a classic paper, Miller and Stanton extensively reviewed the neurological reactions following immunization. These reactions can occur

after the administration of any immunogen but appear to be more common after some vaccines than others. Encephalitis following smallpox vaccine could be severe and in some countries occurred as frequently as 19/100,000 persons of military age receiving a primary vaccination. The Semple vaccine against rabies was also noted for its tendency to cause significant neurological manifestations. Although there was a substantial improvement with the use of duck embryo vaccine, these reactions could also occur with this product as manifested by two cases occurring in Dallas in 1972-1973; the first case had the Guillain-Barre' syndrome, the second case was categorized as disseminated encephalomyelitis. Recognized neurological syndromes following immunization include encephalitis, encephalopathy, disseminated encephalomyelitis, transverse myelitis and peripheral neuropathy which was acute and either localized or generalized. The localized form of acute peripheral neuropathy often had a tendency to involve the brachial plexus. When generalized, the Guillain-Barre' syndrome resulted.

Some vaccines are rarely associated with any neurological side-effects such as tetanus toxoid. Some vaccines had never been associated significantly with neurological reactions, e.g., influenza vaccine. The large number of vaccine doses administered over a short period with intensive surveillance uncovered the association of this vaccine with the Guillain-Barre' syndrome. The occurrence of many different types of neurological syndromes after a latent period and the similarity of the pathological processes that may occur after the administration of equine anti-serum suggested the importance of immunological mechanisms to Miller and Stanton. "The common factor in the pathogenesis of these cases, compromising encephalitic, myelitic, Landry,

Guillain-Barre', radicular, polyneuritic, and mononeuritic syndromes, is anaphylactic hypersensitivity, and that a similar mechanism may be involved in many of the identical neurological illnesses which may occur independently of preceding inoculation." Most vaccines now contain a warning of the potential hazard of neurological reactions which can evidently follow the parenteral administration of any biological substance.

The critical problem that must be faced is that if there is a mandatory rate of untoward side-effects following the administration of any vaccine and if we demand that immunization be accomplished by law before entry into elementary school, who is liable for the consequences of the immunization process. Specifically, if we are to maintain our present freedom from poliomyelitis and faced with the fact that wild-type viruses remain circulating in some portion of society and are added to by imports from abroad, who is responsible for the family in which the father loses his wage earning potential after contact with his son who must be compulsorily immunized before he can enter the first grade. The pharmaceutical firm must be held responsible for errors in manufacture and in warning the recipient of the vaccine of any complications that may accrue from its use. Cutter Laboratories, for its role in the Cutter incident involving poliomyelitis, lost claims amounting to 3 million dollars, two-thirds of which was covered by insurance.

In the United States, aside from liabilities assumed by the federal government for the swine influenza immunization campaign, (claims estimated at $650,000,000) the pharmaceutical company and indirectly its insurer have been the legally responsible parties to which claims have been made. In

Japan and in some European countries, laws have been enacted to provide for compensation from public funds to persons suffering damage from vaccinations which are prescribed or recommended in public by the competent authorities. In these countries a reasonable probability of the causal relationship between the immunization and the injury is regarded as sufficient for payment of damages. In Germany, damages are paid as a pension and this is also the case in Denmark, provided that the disablement is 50% or more. If the disablement is less than 50%, damages are usually paid as a capital sum. Children, however, receive their compensation only after they have reached an age of 15 years. Below this age financial aid can be obtained from public funds under the general social laws.

DIPHTHERIA, PERTUSSIS AND TETANUS

The initial diphtheria vaccine was a toxin-antitoxin mixture followed by a precipitate of toxin and antitoxin. In the 1920's it was learned that treatment of the toxin by formaldehyde resulted in a loss of toxicity but no impairment of antigenicity. Tetanus toxoid vaccines were also prepared by the same inactivation process. At present, there are individual vaccines for each of the toxoids but the majority of immunization is accomplished with the use of adsorbed combination vaccines, diphtheria, pertussis and tetanus (DPT) or tetanus and the adult dose of diphtheria toxoid (Td). Following the introduction and widescale use of these vaccines, the incidence of each of the diseases declined markedly. In conjunction with the fall in diphtheria cases, the prevalence of nasopharyngeal colonization with *Corynebacterium diphtheriae* also fell. It is to be noted that immunization with diphtheria toxoid does not affect the carrier rate for this organism. Although the incidence of pertussis was likewise dramatically affected, the recent occurrence of focal outbreaks of pertussis in several areas of the country (Cincinnati, Ohio and Atlanta, Georgia) indicated that we still have continuing problems with this pathogen. The distribution of tetanus spores in soil and the presumed contamination of wounds with *Clostridium tetani* has not changed since the introduction of the tetanus toxoid vaccine; the vaccine is not preventing infection, in essence, it is preventing only the disease.

The diphtheria epidemic in Austin, Texas and subsequently in San Antonio, Texas in 1968-1969 and 1970-1971 demonstrated the predilection of this

microorganism to cause problems in modern urban areas in the country and particularly in Texas [Table 3]. In San Antonio, in 1970, cases occurred throughout the year with the peak being reached in the late summer [Figure 2]. Cases predominated in the non-vaccinated Latin-American population in the central city area [Figure 3]. Younger children, 1-4 and 5-9 years old, were particularly affected. The case-fatality ratio was low, 1.8%, contrary to the national experience generally in which a constant case-fatality ratio approximating 10% has been the rule. It is probable that in San Antonio the lower case-fatality ratio resulted from earlier recognition and proper treatment of cases in an epidemic situation. There were several phage and biotypes of *Corynebacterium diphtheriae* in the epidemic suggesting that the cases in San Antonio represented an epidemic superimposed on a regular endemic occurrence of the disease. The epidemic waned with the presumptive antibiotic treatment of carriers, publicity about immunization and the movement of immunization teams into affected areas of the city.

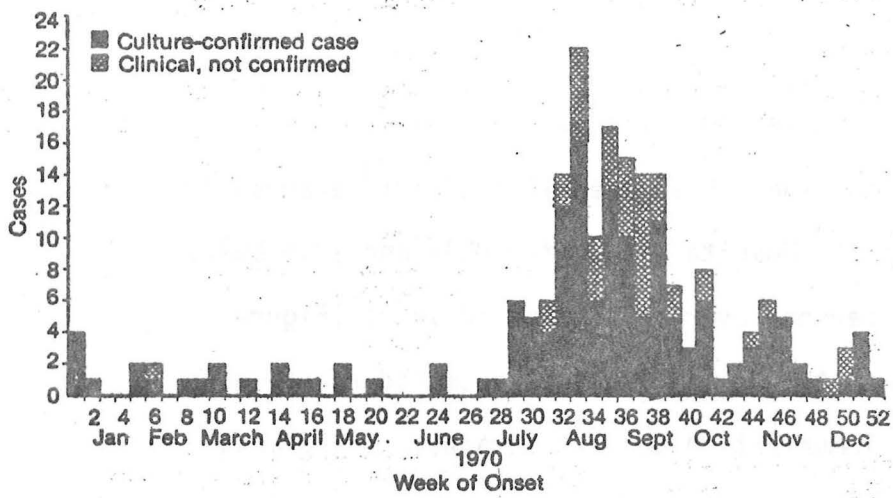
The pertussis problem in the United States may be having a resurgence related to the facts that adult immunity to the microorganism induced through immunization has waned and that pre-school immunization of certain population groups has not been successful. The recent Cincinnati epidemic was centered in the General Hospital and involved adult cases who then spread the microorganism to other adults and to pediatric patients. The disease in adults, now with lapsed immunization, was prolonged and severe with a course which might last 10 weeks accompanied by paroxysms of coughing followed by vomiting and associated with feelings of suffocation. The epidemic in Atlanta, Georgia was a local community outbreak with a total of 115 laboratory

TABLE 3

Percent of Population Fully Immunized Against Diphtheria by Age Group, and Socioeconomic Status, San Antonio, Bexar County, Texas 1969

AGE GROUP IN YEARS	SOCIOECONOMIC CLASS			TOTAL FOR CITY OF SAN ANTONIO
	LOWER	MIDDLE	UPPER	
1 - 4	60	58	85	67
5 - 14	28	24	49	33
15 - 39	24	23	35	27
40 +	11	15	25	18

Diphtheria Surveillance, CDC 1969-70, Summary



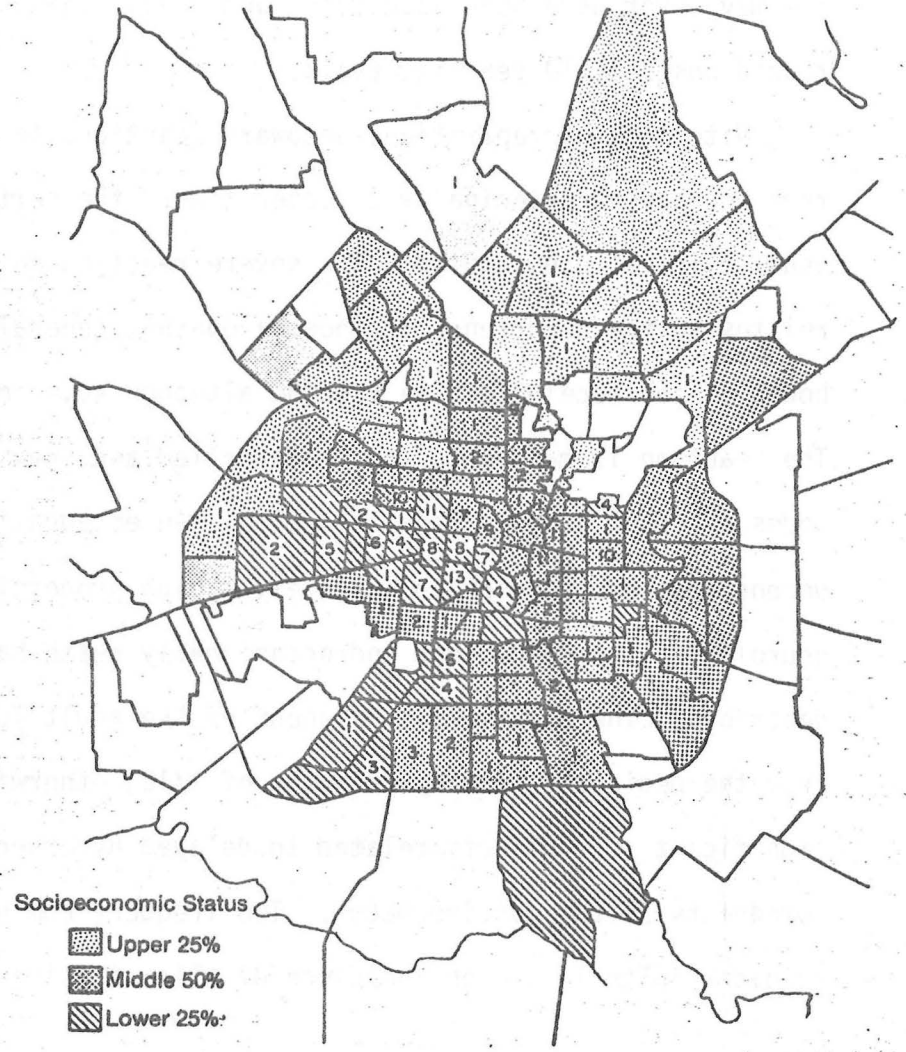
Distribution of 196 diphtheria cases by week of onset and culture results, San Antonio, 1970.

Figure 2

J. Am. Med. Assn. 224:306,1973

Figure 3

J. Am. Med. Assn. 224:307, 1973



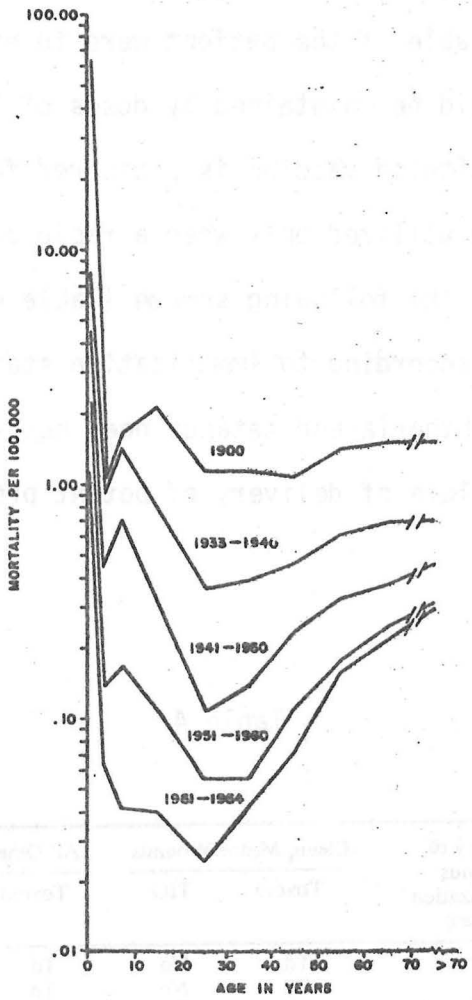
Number of diphtheria cases by census tract and socioeconomic status, San Antonio, 1970.

documented cases occurring in the period April-October, 1977.

Since 1970 in Dallas, Texas there have been 11 cases of tetanus; 9 hospitalized at Parkland Memorial Hospital, 1 at the DVAH and 1 at BUMC. All of the cases occurred in persons over the age of 50 years [Figure 4]. The initiating injury often was trivial and the patients had received no immunizations or at most one immunization against tetanus. In Dallas, neonatal cases have declined and cases in addicts have not yet been a problem. The difficulty with tetanus in this city at the present time rests in the primary immunization of older adults (3 doses of vaccine) who may never have been vaccinated and in maintaining immunity by booster toxoid doses at 10 year intervals.

With modern preparation, untoward reactions to DPT or Td vaccines are rare and appear principally directed toward the pertussis component. The usual clinical presentation of a severe reaction following pertussis vaccine relates to the occurrence of encephalopathy, generally coming on within 24 hours of the receipt of the vaccine although sometimes delayed for 2-3 days. The reaction is manifested by uncontrolled and unexplained screaming episodes or convulsions without sequelae. An encephalitis-like syndrome of unconsciousness, prolonged seizures, a high proportion of persistent neurological complications and occasionally death has infrequently been described. The diphtheria component of the adult Td vaccine is reduced from the pediatric dose by a factor of 1/10; otherwise, in the adult, significant side-effects related to delayed hypersensitivity reactions to components of the vaccine occur. Too frequent administration of tetanus toxoid results in a high incidence of allergic side-reactions.

Figure 4



Average Annual Tetanus Mortality Rates, According to Age Group, United States, 1900 and 1933-1964.

N. Engl. J. Med. 280:570, 1969.

Reliable immunity cannot be expected to occur after the clinical disease of diphtheria or tetanus. After the clinical illness, the patient must be primarily immunized. If such immunization does not take place, the physician may be liable if the patient were to experience another attack. Adult immunization should be maintained by doses of Td vaccine every ten years. The alum precipitated vaccine is preferred for routine immunization with fluid toxoid being utilized only when a rapid burst in antibody formation is required. The following scheme [Table 4] depicts tetanus immunization schedules according to immunization status and type of injury. In Western society, diphtheria and tetanus need never occur. The fact that they do points to a failure of delivery of potent protective immunogens to the population.

Table 4

History of Tetanus Immunization (Doses)	Clean, Minor Wounds		All Other Wounds	
	Toxoid	TIG	Toxoid	TIG
Uncertain	Td	No	Td	Yes
0-1	Td	No	Td	Yes
2	Td	No	Td	No‡
3 or more	No§	No	No‖	No

* TIG = human tetanus immune globulin; Td = Tetanus and Diphtheria Toxoids.

‡ Unless wound more than 24 h old.
§ Unless more than 10 years since last toxoid dose.
‖ Unless more than 5 years since last toxoid dose.

WOUND MANAGEMENT FOR TETANUS*

Ann. Intern. Med. 85:622, 1976

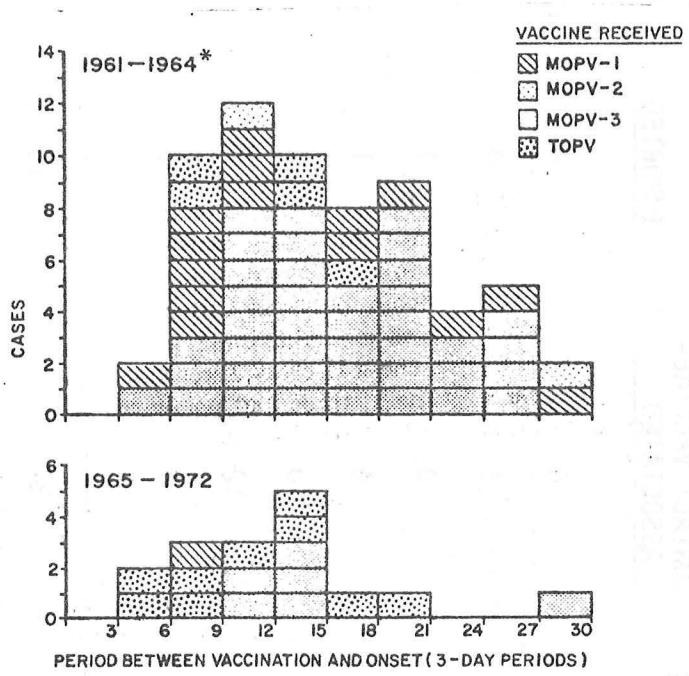
POLIOMYELITIS

The major event in the control of poliomyelitis was the cultivation of the virus in tissue culture by Enders, Weller and Robbins, an achievement for which they were awarded the Nobel Prize. Later, Salk developed a formaldehyde inactivated vaccine utilizing the three poliomyelitis virus types. Koprowski, Cox and Sabin worked to produce a live attentuated vaccine with the Sabin strains of virus eventually being accepted as those that would be produced and distributed. The Salk inactivated poliomyelitis vaccine (IPV) was field-tested in 1954 in the Francis Field Trial. It was licensed for production shortly thereafter with six pharmaceutical firms making the vaccine. Early, the delivery of IPV was faulted by the occurrence of the Cutter incident. Later, it was recognized that the formaldehyde inactivation process was insufficient to destroy one common contaminant of primary kidney tissue culture, viz., SV 40, a papovavirus, which has been shown to have oncogenic potential. Fortunately, in follow-up studies of persons given SV 40 virus inadvertently, there was no evidence that this virus, in fact, did produce tumors although it could be shown by serological means that infection had occurred. IPV was later replaced in the United States and most other countries (excluding Sweden & Finland) by the Sabin Vaccine [oral poliomyelitis vaccine, monovalent and trivalent (MOPV and TOPV)]. The Cutter incident had emphasized the need for surveillance for complications following the introduction of any new vaccine. Such surveillance techniques eventually culminated in the discovery of a rare but definite complication of OPV, i.e., vaccine associated poliomyelitis. Such

cases could be classified as occurring in the recipient of the vaccine, the household contact of the recipient of the vaccine, or the community contact of the recipient of the vaccine [Figures 5,6]. The original report documenting the occurrence of vaccine associated cases of poliomyelitis stressed their infrequent occurrence, the different epidemiological pattern of these cases as opposed to those occurring after natural infection and the fact that the majority of cases could be related temporally to feeding type 3 MOPV. In the 1964 study, 46/57 compatible cases occurred in men and 25/46 male cases were in age groups 15-39. It was also estimated that after feeding type 1 MOPV, there were 0.17 cases per million doses of vaccine administered while after type 3 MOPV, there were 0.40 cases of vaccine associated poliomyelitis per million doses. The Special Advisory Committee appointed by the Public Health Service recommended a change in the order of MOPV feeding to infants 2 followed by 1 followed by 3, and that routine immunization of adults not be performed if those persons had not previously been immunized. The control of poliomyelitis would depend on the routine immunization of infants and children; adults would be primarily immunized only if they were in high risk population groups or if travel to endemic areas was planned. In the years subsequent to that report, MOPV has essentially been replaced by TOPV. The type 3 vaccine strain has been replaced by a further attenuated variant. IPV in the United States is no longer available for use.

As a result of these changes in the use of the vaccine coupled with the changing epidemiology of poliomyelitis, there exists now the following set of problems [Table 5]: 1) Although epidemic situations are now distinctly unusual, a type 1 poliomyelitis epidemic did occur in 1970 along the Texas-

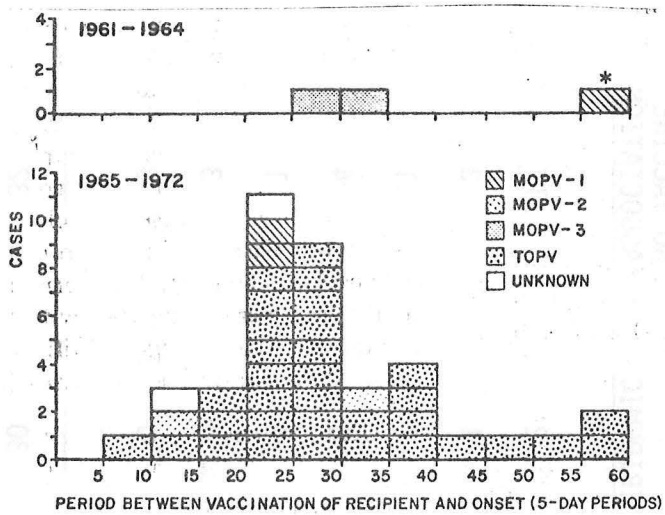
Figure 5



Recipient cases of poliomyelitis, by period between vaccination and onset of illness, United States, 1961-1964 and 1965-1972. *Excludes one agammaglobulinemic patient with a probable 40-day interval (MOPV-1) or a possible 5-day interval (MOPV-3).

Am. J. Epidemiol. 104:202, 1976

Figure 6



Contact cases of poliomyelitis, by period between vaccination and onset of illness, United States, 1961-1964 and 1965-1972. * A close contact received MOPV-3 also 18 days prior to onset; Type 1 poliovirus was isolated from the patient.

Am. J. Epidemiol. 104:202, 1976

Table 5

PARALYTIC POLIOMYELITIS CASES, BY AGE GROUP AND

EPIDEMIOLOGIC CLASSIFICATION, UNITED STATES, 1969-1976

AGE	EPIDEMIC	NO VACCINE ASSOCIATION	VACCINE-ASSOCIATED RECIPIENT	CONTACT VACCINE-ASSOCIATED	IMPORTED	IMMUNE DEFICIENT
< 1 - 4	22	17	8	6	8	10
5 - 9	1	3	1	1	0	0
10 - 14	1	1	0	0	1	0
15 - 19	6	4	1	4	1	0
20 - 29	0	1	0	10	2	1
30 - 39	0	3	0	12	1	0
40 +	0	3	0	1	2	0
TOTAL	30	32	10	34	15	11

Polio Surveillance
Center for Disease Control, 1974-76

Mexican border eventually causing 22 cases; in 1972 an epidemic occurred in a Christian Science School in Connecticut with 8 associated cases. The potential of an epidemic in most parts of the country persists particularly since there has been a persistent problem with respect to the immunization of pre-school children. 2) Imported cases. In the interval 1969-1976, there were 15 imported cases into the United States. With respect to Texas, Mexico was the source of origin of 14 of the imported cases. 3) Endemic cases, non-vaccine associated. Thirty-two cases occurred in the United States outside of epidemic situations in the interval 1969-1976. Some of these cases are most probably related to vaccine viruses. 4) Vaccine-associated cases. Since the 1964 report, there has been a change in the ratio of vaccine recipient cases to the number of cases in contacts of the vaccine recipients. At the present time, that ratio is 10/34, with the majority of vaccine related cases now occurring in contacts of vaccine recipients. Evidently, TOPV feeding with a more attenuated strain of type 3 poliomyelitis virus with emphasis on immunization of infants and children has resulted in a shift of vaccine-associated cases to contacts of the recipients of the vaccine, particularly those in the 20-39 year age group. Practically, this would result in an increased risk to non-immunized parents of young children who would undergo immunization routinely and then on a mandatory basis on entrance into school. There are a cohort of persons entering young adulthood who have not been immunized against poliomyelitis. Since IPV is no longer available for use, a persistent problem relates to the management of such young parents. This is a particularly pertinent problem since during 1977 the ratio of non-vaccine/vaccine associated cases was 14/4. It has now been recommended as

part of a national strategy against poliomyelitis, that IPV be made available on a limited basis to initiate some quantity of immunity which might then be completed by IPV or the regular course of OPV. 5) Cases of poliomyelitis in immune deficient persons. During the interval 1969-1976, there were 11 such patients including 5 deaths. The majority of such persons had exposure to OPV either as a recipient or as a contact of the recipient. The interval between exposure to the vaccine virus and the onset of illness was prolonged in several of the cases, suggesting either infection with a wild-type virus or altered pathogenesis. It has now been reported that in immune deficient persons the vaccine virus may produce subacute and chronic changes and virus can be isolated from the central nervous system months after the onset of illness.

Since poliomyelitis virus of one type may interfere with the growth of the other types in the human gastrointestinal tract, it is necessary to give 3 doses of OPV in order to insure immunity. In infants, immunization is begun at 6-12 weeks of age with the second dose of vaccine given 6-8 weeks later. A third dose of vaccine is given at approximately 1 year of age and a booster dose is given upon entrance into school. Additional doses do not appear to be necessary unless persons are entering into high risk situations when a single dose of OPV is given. Oral poliomyelitis vaccines today are produced in monkey tissue cultures. A vaccine has been produced in WI-38 cells and has been used extensively abroad. The cellular substrate has been well defined for the WI-38 cells and it is for this reason as well as the limited quantities of non-human primates, that this vaccine may eventually replace the presently available ones that have been grown in monkey kidney tissue culture.

RUBEOLA

Rubeola is a significant cause of morbidity in childhood. It can induce true viral pneumonia (giant cell pneumonia) and paves the way for bacterial suprainfection of the lung and such structures as the middle ear. Encephalitis follows in 1/1000 cases of the disease, has a high case-fatality ratio (40%) and survivors are left with significant sequelae. Following a long latent period, measles virus infection of the brain may become manifest as subacute sclerosing panencephalitis, an infrequent but uniformly fatal disease of middle childhood. The rate of subacute sclerosing panencephalitis following measles has been estimated to be 5.2 - 9.7 cases per 1,000,000 estimated cases of measles.

Enders and Peebles first isolated rubeola virus in tissue culture in 1953. Ten years later the first live attenuated viral vaccine against measles (Edmonston B strain of virus) was licensed for use in the United States. In 1960-1961, a killed virus vaccine was introduced and used for approximately 2 years before it was withdrawn. The original live virus vaccine was highly reactogenic; an injection of gamma-globulin had to be given concurrently to suppress the severity of the side-reactions. Later, more attenuated virus strains were developed and the administration of gamma-globulin was no longer needed with these vaccines. During the early phases of administration of the vaccine, data had not been derived concerning the optimal age at which to deliver the vaccine. Ideally, the child should be free of maternally transmitted antibody and should have sufficient immunological maturity to be able to respond appropriately with a long-lived response when the vaccine was administered. The vaccine is

dispensed in a lyophilized form. After reconstitution with sterile water, it has a limited life span (8 hours) when kept at 4°C. It is probable particularly in the early history of the vaccine, that this product was delivered in an inactivated form to some percentage of the pediatric population.

To induce immunity, several injections of the killed vaccine were necessary. The live attenuated vaccine could be given in a single dose. With the licensure of the vaccine, the first persons immunized and at the most intensive level tended to be the young children of middle and upper socioeconomic class families. Rubeola, although diminished in incidence, still occurred in the central cities with the majority of cases in pre-school children. The diminished incidence of rubeola fostered through immunization allowed many children to escape natural measles and yet these same children were often considered to be too old to be immunized. The federal government also gave grant support to rubeola immunization programs. With the withdrawal of such grant support, the time was right for a re-surgance of measles which occurred in 1970-1971. In that year, Dallas, Texas experienced an epidemic which resulted in 1,071 cases of the disease and 3 deaths [Figure 7]. In that epidemic, attack rates for young children tended to be higher in blacks. With increasing age, cases tended to be increasingly more common in white children. This situation reflected the fact of ongoing transmission of rubeola in ghetto neighborhoods but the relative non-involvement of middle and upper socioeconomic class neighborhoods. With the occurrence of an epidemic, the circulation of rubeola virus spilled in these neighborhoods affected those children too old to have been immunized

and too young to have incurred natural measles. The resurgence of measles in Texas coupled with the recent epidemics of diphtheria in Austin and San Antonio in 1968-1970 prompted the Texas State legislature to pass immunization laws requiring that the child entering elementary school must have an adequate immunization status against diphtheria, pertussis, tetanus, poliomyelitis, rubeola and rubella. Reflecting the eradication status of smallpox, this immunization no longer was required. The 1970-1971 resurgence of rubeola and subsequent events pointed out the following: 1) Killed measles vaccine was inadequate; persons receiving this vaccine and experiencing natural measles challenge might develop "atypical measles". These children had to be immunized again with the most modern vaccine. 2) Children receiving gamma-globulin with the Edmonston B strain of vaccine could not reliably be counted on to be protected and hence had to be immunized again. 3) Children vaccinated at an early age (less than 12 months of age) were not reliably immunized and hence should be reimmunized. 4) Some children were vaccine failures most probably related to the fact that in actual use the vaccine virus may have been inactivated. Still, given the fact that some children particularly in the early history of the vaccine were not immunized correctly, the vaccine proved itself to be effective at a 95% level. Follow-up studies on children immunized adequately reveals a persistence of hemagglutination inhibition test antibody although at a lower level than that seen after natural measles [Figure 8].

The events as recorded above create the present epidemiological situation with respect to rubeola. Pre-school children particularly in the central cities continue to be inadequately protected against the disease.

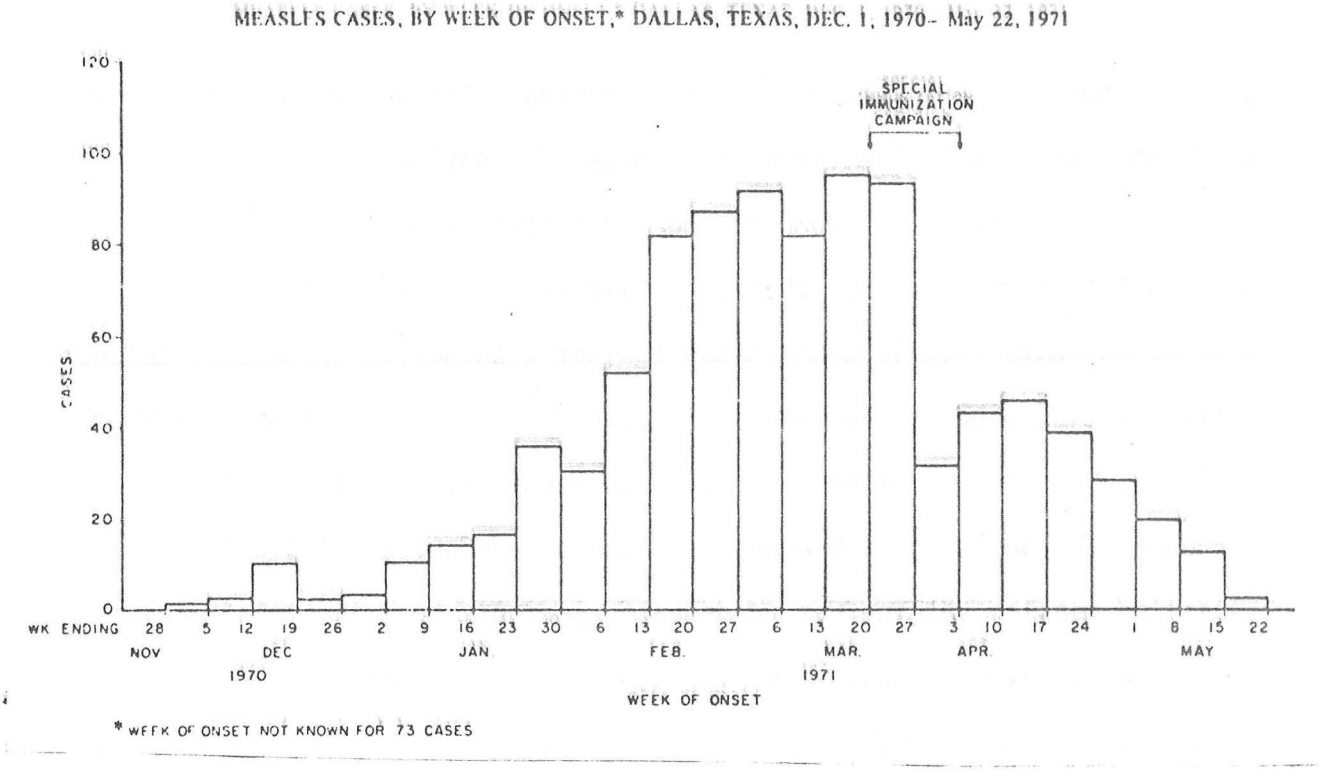
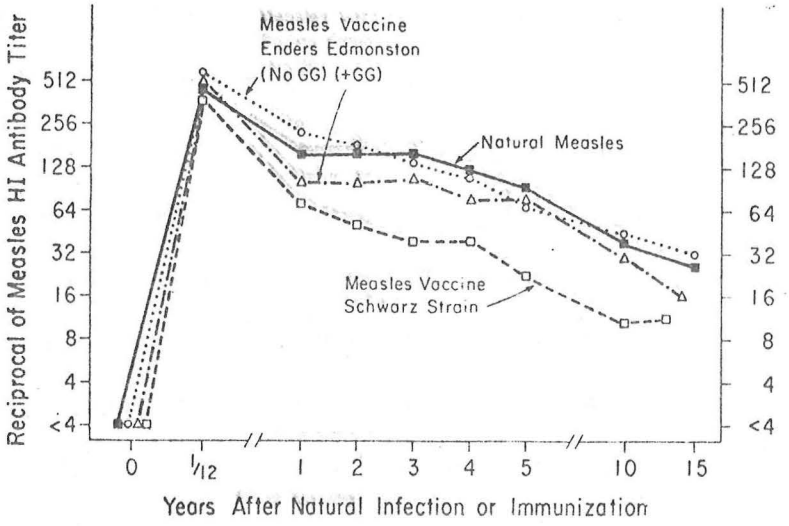


Figure 7



Measles antibody reponse and persistence after natural infection and immunization: A 15-year follow-up.

Figure 8

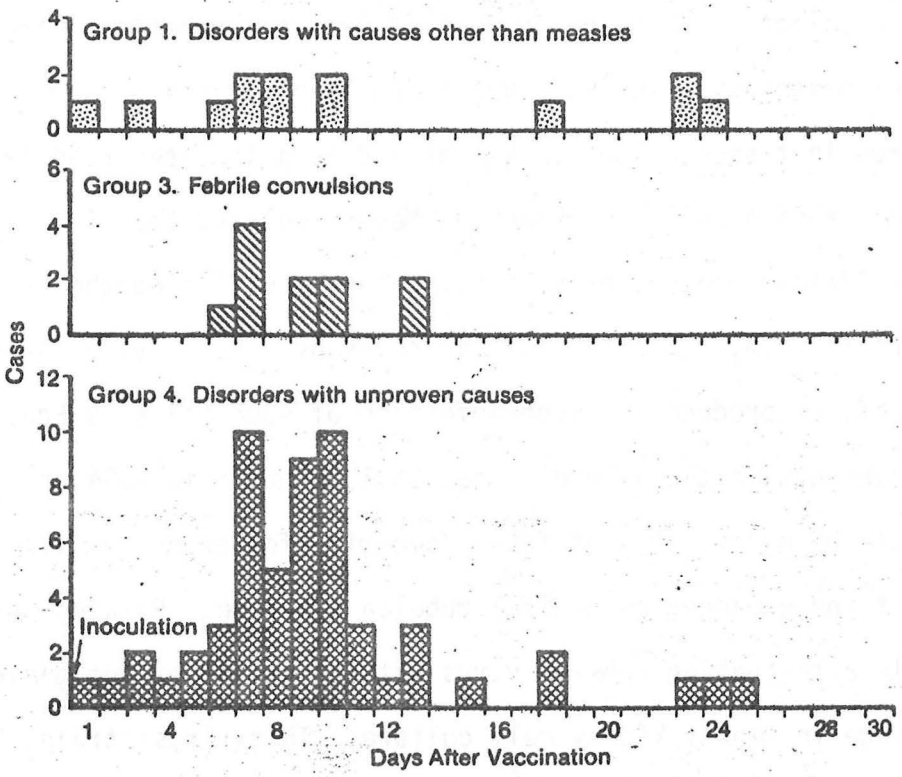
Entrance into school markedly improves the immunization status of the children due to the legislated mandatory immunization statute. Children often from middle and upper socioeconomic class neighborhoods and rural areas may now be inadequately protected against rubeola and as a consequence for the next several years measles in the young adult may become an increasing problem. This is now manifest by outbreaks of rubeola in middle and high schools, colleges and recruit populations. The problem is compounded by the fact that we live in a mobile society and the exact manner in which a child has been immunized is not accessible for review and persons may think that they have had measles when actually they were experiencing another exanthematous eruption. Younger physicians, not having seen measles in their training, may also be unskilled in diagnosing cases. Measles in the young adult promises to be an increasing problem and at present we have insufficient knowledge to plot its clinical course.

Children vaccinated with the killed virus vaccine on reexposure to the live virus vaccine or natural measles virus experience local reactions of unusual severity at the site of the inoculation of the vaccine or "atypical measles". Atypical measles consists of the clinical configuration of a maculopapular eruption with vesicular and purpuric components beginning on the extremities and spreading centrally along with pulmonary consolidation and pleural effusion accompanied with an eosinophilic reaction. Viral antibody titers rise and fall as expected but the virus cannot be recovered from the respiratory tract. The areas of pulmonary consolidation are not bacterial in etiology. The genesis for these alterations is not clear but it is known that the killed virus vaccine elicited antibody only to the

hemagglutinin of the virus and not to the hemolysin. The pathogenesis of the disorder most probably involves some component of delayed hypersensitivity responses.

Moderate fever may occur during the month after immunization. Generally, rash, fever, or both appear between the 5th and 12th days. Rash when it occurs is usually minimal without generalized distribution. More serious yet apparently rare is the occurrence of neurologic disorders following live measles virus vaccination [Figure 9]. From 1963 through 1971, 84 cases of neurologic disorders with onset less than 30 days after live measles virus vaccination were reported in the United States. Thirteen could be adequately accounted for by causes other than vaccine, and another 11 were uncomplicated febrile convulsions probably related to vaccination. One case met diagnostic criteria for subacute sclerosing panencephalitis. The remaining 59 showed clinical features of encephalitis or encephalopathy. Causes of these cases could not be established, but 45 (76%) had onset between 6 and 15 days after vaccination; this clustering suggests that some may have been caused by vaccine. The estimated incidence of the reported neurologic disorders as 1.16 cases per million doses of the vaccine.

Figure 9



Neurologic disorders following live measles vaccination, by day of onset after inoculation (1963 to 1971).

J. Am. Med. Assn. 223:1460, 1973

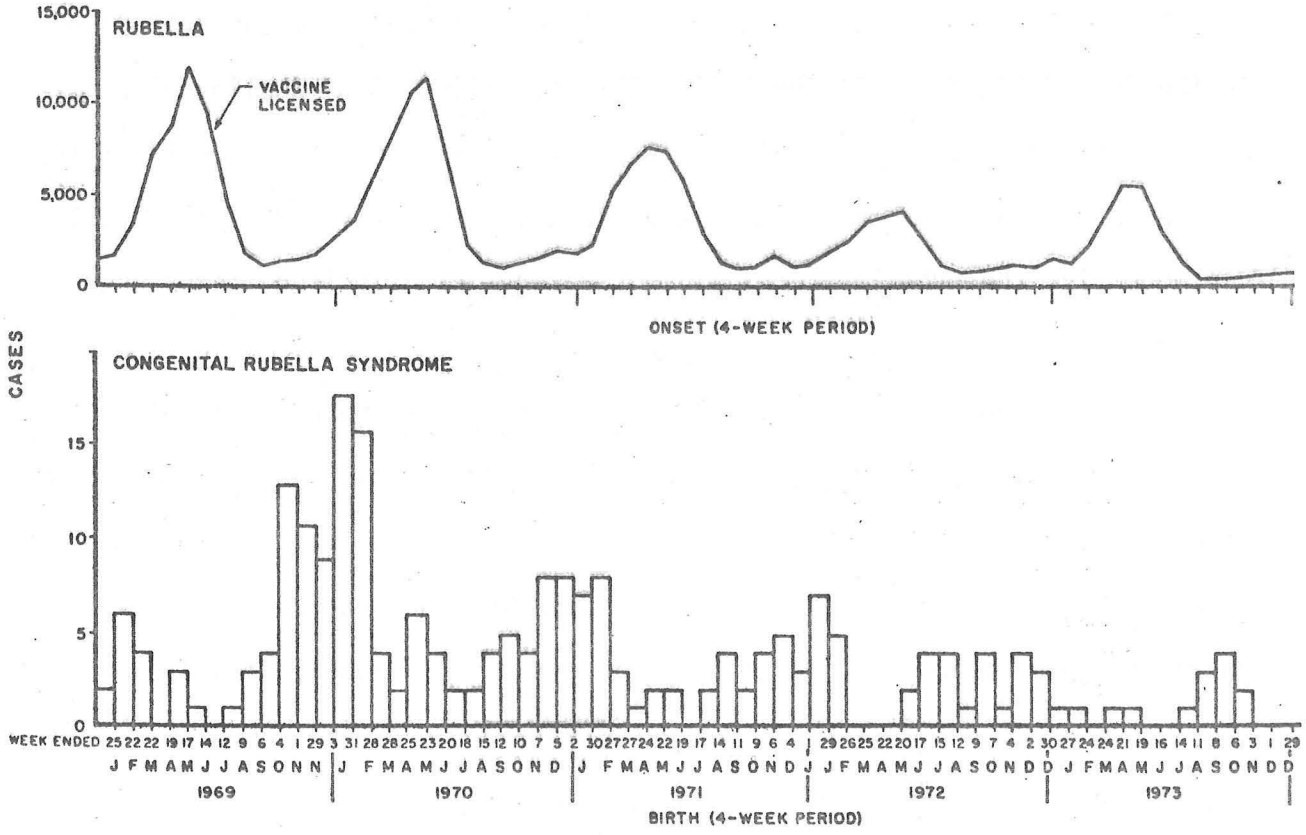
RUBELLA

Long recognized as a clinical entity, rubella was considered to be an innocent disease of childhood. In 1941, in a classical treatise, Sir Norman Gregg, an Australian ophthamologist recognized the association between congenital cataracts and the occurrence of maternal rubella in the first trimester of pregnancy. In 1962, two independent groups of workers isolated rubella virus in tissue culture. Weller and Neva isolated rubella virus in primary human amnion cells; Parkman and Meyer isolated the virus in primary cultures of African green monkey kidney cells by utilizing the principle of interference, i.e., infection of the cells by rubella virus prevented the cytopathic effect produced by suprainfection of such cells by Echo 11 virus. These achievements in the wake of a national epidemic in 1964 gave rise to knowledge of the exact rates of fetal deformity following rubella and to awareness of the expanded congenital rubella syndrome. Parkman and Meyer succeeded in attentuating rubella virus without a loss of antigenicity by serial passage in monkey kidney cell culture. This virus strain, HPV-77, was then passaged in duck embryo and dog kidney cell tissue culture giving rise to two vaccines which were suitable for human trials. European workers succeeded in attenuating rubella virus by passage in rabbit kidney tissue culture eventually producing the Cendehill virus vaccine. Plotkin and associates produced an attenuated virus in WI-38 cells, the RA 27/3 vaccine strain. The vaccine virus produced in dog kidney cells was later withdrawn when it was found that this product engendered a high rate of arthralgias and arthritis as side-effects. The RA 27/3 vaccine is not presently available

for use in the United States although it is thought that eventually it may replace the other vaccines because it is produced in a defined cell substrate and gives rise to higher and more sustained serum neutralizing antibody levels.

The vaccine strategy in the United States differed from that utilized in the United Kingdom. In the United States, nation-wide rubella epidemics occur at 6-9 year intervals. After the 1964 experience, it was realized that another wide-scale epidemic might take place in the early 1970's [Figure 10]. Consequently, the rubella immunization strategy in the United States consisted of administering rubella vaccine to children 1-9 years of age with the added provision that women entering the child-bearing age range be tested for rubella immunity by the hemagglutination inhibition (HAI) test. Women who were HAI test negative then would be immunized provided that they would adopt means to avoid pregnancy for two months following vaccination. In the United Kingdom, primary reliance on the prevention of rubella centered on the detection of HAI test negative teen-aged girls and women and their subsequent immunization provided that they avoided pregnancy in the ensuing two months. In the United States, the incidence of rubella and the occurrence of the congenital rubella syndrome has declined markedly. However, there is now a cohort of persons reaching adolescence and young adult life that have escaped natural rubella infection and were beyond the age group to have participated in the vaccine campaigns. Widespread immunization essentially dampened the occurrence of rubella so that these persons escaped natural infection. As a consequence of these events and the new knowledge that rubella could spread in populations despite the presence of "herd immunity", rubella epidemics now occur regularly in high school, college and recruit

Figure 10



Cases of rubella (official telegraphic reports from states and areas) by period of onset and of congenital rubella syndrome by period of birth (from CRS registry) in the United States, 1969 to 1973.

Pediatrics 55:20, 1975

populations. It is estimated that until the effect of mandatory immunization laws can be realized, at least 15% of young women will continue to be non-immune with respect to rubella. In order to maintain our relative freedom from the occurrence of the congenital rubella syndrome, immunization of HAI test negative women is essential. A new serological test, employing the principle of passive hemagglutination (Rubacell, Abbott Laboratories) is less expensive to perform than the standard hemagglutination inhibition test and may be more widely employed generally to detect non-immune women. Times of life that appear practically suited for testing rubella immunity in young women include pre-marriage serological testing, initial visits of young women to the obstetrician-gynecologist and the post-partum period. This latter period is also suitable for immunization although the injunction to avoid pregnancy for the two months following vaccination remains.

The immunity following rubella is reflected in serum neutralizing antibody test titers which in turn correlate well with the standard HAI test. After rubella immunization, approximately 95% of persons develop antibody detectable by the hemagglutination inhibition test technique. The serum level of antibody is less than after natural rubella infection. Complement fixation test antibody titers rarely become positive after rubella immunization although these titers are raised transiently following natural rubella infection. The rubella vaccine was licensed in 1969 and it is too early to state definitively how long immunity will last following administration of the vaccine. In children, not exposed to reinfection, developing relatively high antibody test titers, serial studies have shown no tendency for antibody levels to decline significantly. Those developing lower antibody test titers have in certain

studies shown some tendency for antibody levels to become non-detectable with time although these children generally have an anamnestic boost in titer when reimmunized. It is known that in persons naturally immune to rubella that reinfection can occur. Reinfection in rubella vaccine recipients has also been demonstrated; however, it is recognized that viremia does not occur in such persons and if they excrete virus into the nasopharynx, it is usually of low titer and does not pose a significant hazard for transmitting the infection to other persons. Persons receiving the vaccine rarely if ever transmit the vaccine virus to close contacts.

Side-effects related to receiving the vaccine are few in number [Table 6]. Approximately 5% of persons, particularly young women will develop transient arthralgias or arthritis. These usually subside in 1-3 days although on occasion arthralgias may persist for a longer period. Persons receiving the vaccine may develop signs and symptoms related to peripheral neuropathy with paresthesias. Children may assume a characteristic stance, the "catcher's crouch", in order to alleviate the symptoms. These latter symptoms may develop at a later period following immunization. The major problem with the vaccine lies in its potential capacity to infect the fetus and be teratogenic. Therein lies the reason why pregnant women should not be vaccinated or should avoid pregnancy for the two months following immunization. In studies on aborted fetuses, it has been demonstrated that the vaccine virus can be recovered from tissues of the fetus including structures such as the eye. However, a limited number of women who had inadvertently been vaccinated during pregnancy and who were non-immune at the time of vaccination, have been brought to term with the delivery of normal children. This number is

small and does not exclude the fact that the vaccine virus may be a minor teratogen. Given the fact that a certain rate of congenital abnormalities is present accompaniment of pregnancy, it is possible that such abnormalities may be ascribed to the vaccine, with subsequent liability then falling on the manufacturing pharmaceutical firm or potentially the physician. Consequently, if a woman is pregnant at the time of the administration of the vaccine and if it can be ascertained that at that time she is HAI test negative, standard medical practice dictates advising the patient to undergo a therapeutic abortion. If the pregnancy is a desired one or the patient is older, the risks must be explained to the patient. Under such circumstances and with full informed consent, the pregnancy can be brought to term with the understanding that malformations related to vaccine virus infection cannot be excluded.

Table 6

Incidence and Characteristics of Reactions to Rubella Vaccines: Study 1, New Orleans

	Cendehill Vaccinates		HPV-77 DE-5 Vaccinates		Prospective Controls		Retrospective Controls	
	No.	%	No.	%	No.	%	No.	%
No. sampled	1,000	...	1,000	...	557	...	1,045	...
Respondents	828	82.8	821	82.1	438	78.6	1,045	100.0
All reactors	74	8.9	60	7.3	25	5.7	7	0.7
Joint and muscular symptoms	60	7.2	42	5.1	21	4.8	7	0.7
Arthritis	7	0.8	5	0.6	5	1.1	2	0.2
Paresthesia	32	3.9	25	3.0	8	1.8	0	0
Median onset (weeks after vaccination)								
Joint and muscular symptoms	2		2		4		...	
Paresthesia	2		3		3		...	
Median duration (days)								
Joint and muscular symptoms	1-3		1-3		1-3		7-9	
Paresthesia	1-3		1-3		<1		...	

J. Am. Med. Assn. 220:1570, 1972

INFLUENZA

The 1918-1919 pandemic of influenza, one of unusual severity, was termed the "great plague" because it was the cause of an estimated 20,000,000 deaths. In 1933, Laidlaw, Andrewes and Smith isolated the agent of influenza by inoculation in ferrets. An inactivated influenza vaccine was developed and given to service personnel during the world war. During the initial phases of the history of inactivated influenza vaccine, results were often unpredictable because of the lack of appreciation of the extent of antigenic drift (changing antigenic character of the virus between pandemics) and the occurrence of antigenic shift (major change in the antigens of the virus occurring on the average once a decade). The vaccine also contained substantially more impurities than the ones prepared today which are concentrated by zonal ultracentrifugation techniques. The conclusions reached in the earlier studies demonstrated that the vaccine was effective in the neighborhood of 75% protection against illness if the antigenic constitution of the vaccine was similar to the virus which circulated during the season and caused natural infections. With recognition of the phenomena of antigenic drift and antigenic shift, vaccine strategy changed so that each major antigen was included in the vaccine (polyvalent vaccine). At the present time, the following major antigenic types of virus are recognized to have circulated in the world's population: $H_{sw}N_1$, H_0N_1 , H_1N_1 , H_2N_2 and H_3N_2. According to theorists advancing the use of the polyvalent vaccine, that vaccine would contain all seven hemagglutinin and neuraminidase antigens. In the late 1940's and the 1950's, fewer numbers of antigens were recognized

but the same reasoning applied. These early polyvalent vaccines were not successful for two reasons: 1) The extent of antigenic drift away from the prototype virus during the course of the decade might be relatively great. For example, A/Texas is significantly different than A/Hong Kong, the prototype H_3N_2 virus. 2) Local and systemic side-effects limited the amount of total antigen that could be included in the vaccine. The serological response and accordingly the protective effect was directly related to the antigenic mass included in the vaccine. Adjuvants enhanced the serological response to a given quantity of antigen but at the time that the early polyvalent vaccines were being used, such adjuvants were also associated with significant side-effects. The polyvalent vaccine concept is being advanced for use today coupled with the addition of safer adjuvants due to the unexpected transient circulation of A/New Jersey, $H_{sw}N_1$, and the more recent appearance of A/USSR, a H_1N_1 variant.

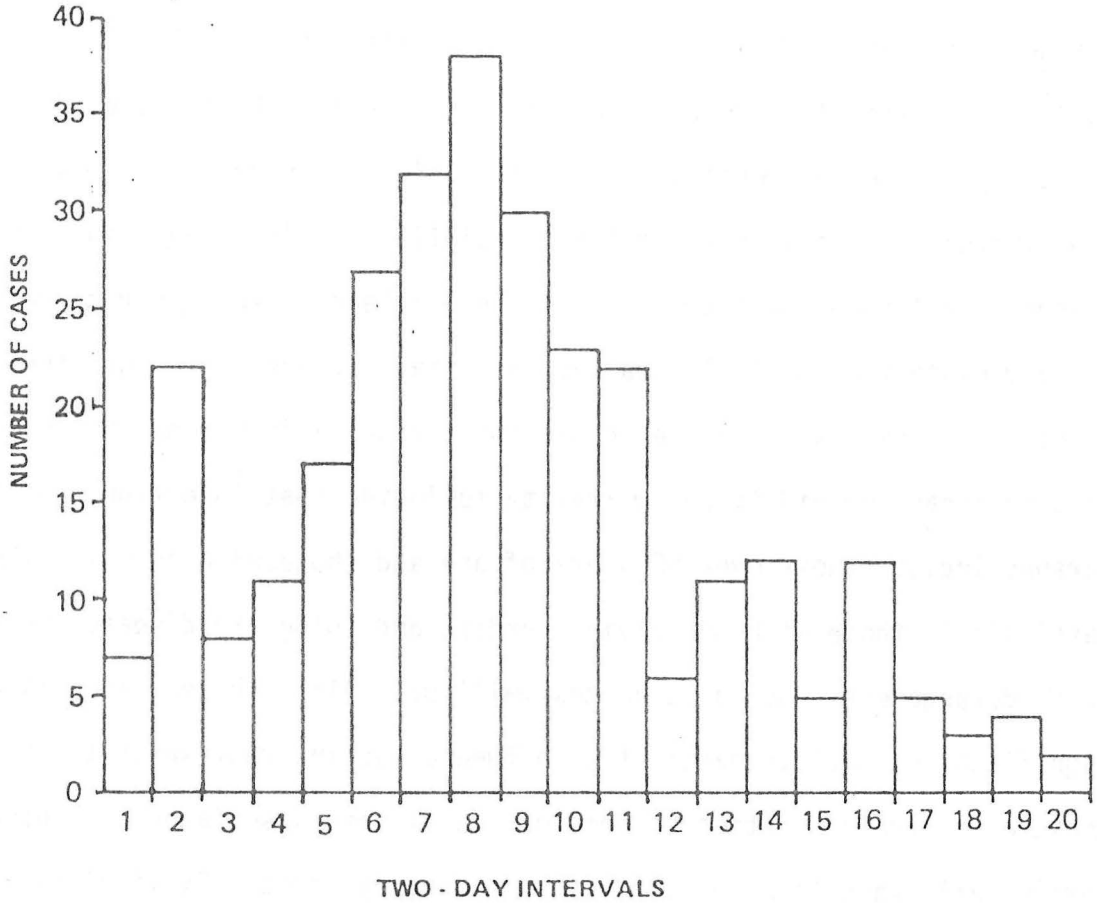
Following demonstration of the ineffectiveness of the polyvalent vaccines in routine yearly usage, univalent, bivalent or at the most trivalent vaccines were prepared. The antigenic constitution of the vaccines is a matter of considerable importance and debate. Constituting the vaccine correctly depends on the capacity to predict the coming year's circulating strain of virus. This in turn depends on effective and adequate surveillance techniques. In general, it has been thought that influenza A strain will circulate in the population against which that population had the least amount of collective immunity. Once a decade a major shift in antigens would occur; if that new virus was capable of circulating in the population, it would succeed the others, replacing them and producing pandemic disease. Those generalizations

were sufficient to predict successful vaccines through the 1960's and the 1970's. It was this generalization upon which the Swine influenza campaign was predicated. The subsequent failure of the $H_{sw}N_1$ virus to circulate in the population at large and the unexpected emergence of A/USSR demonstrates the inherent difficulty of forecasting the next strain of influenza virus that will cause disease in the population.

Prior to the swine influenza campaign, it was believed that the influenza vaccine, aside from causing local and systemic side-effects such as fever and myalgias and occasional allergic side-reactions, was innocuous as far as serious, long-range consequences were concerned. Prior to the cessation of the campaign to immunize the majority of the adult population in the United States, 42,783,707 doses of vaccine had been given. The campaign was halted on or about December 17, 1976. Through February 4, 1977 [Figure 11], a total of 342 cases of the Guillain-Barre' syndrome that had been vaccinated with a vaccine containing A/New Jersey were reported. During the same period, there were 314 cases of the syndrome in unvaccinated persons. There were 29 cases in persons receiving a different influenza vaccine (B/Hong Kong) or in whom the vaccination status was unknown. The onset of the Guillain-Barre' syndrome occurred most commonly 2-3 weeks following immunization. The age group with the highest relative risk were persons aged 25-44. The age group having the lowest relative risk were persons in the 18-24 year age category. The case-fatality ratio in vaccinated and unvaccinated persons developing the syndrome was similar and approximated 4%. Rates for the Guillain-Barre' syndrome varied across the country with Pennsylvania reporting 18 cases in vaccinated persons and

Figure 11

GUILLAIN - BARRÉ SYNDROME BY 2 - DAY INTERVAL BETWEEN DATE OF VACCINATION AND DATE OF ONSET, UNITED STATES OCTOBER 1, 1976 – FEBRUARY 4, 1977



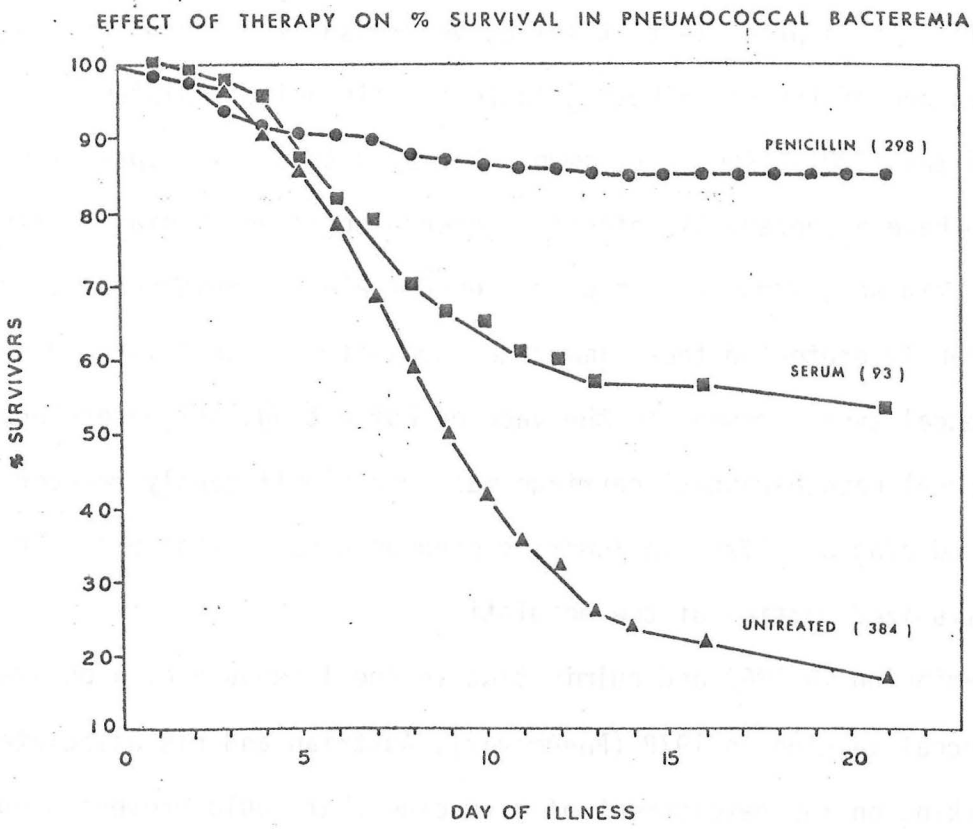
6 cases in unvaccinated persons. Texas reported 8 cases in unvaccinated persons, 1 case in which the symptoms of the syndrome had begun before the administration of the vaccine and 1 case in a person whose vaccination history was unknown. It is now estimated on the basis of the figures given above that 1 case of Guillain-Barre' syndrome can be expected for every 80,000 persons given influenza vaccine. Prior to the swine influenza immunization campaign, there were no reports of association of the syndrome with influenza vaccine. Miller and Stanton's treatise on neurological syndromes following immunization does not mention the occurrence of the syndrome following influenza immunization. This article does point out,however, that the syndrome can be seen after the inoculation of almost any biological product. Although the occurrence of the Guillain-Barre' syndrome complicates the administration of influenza vaccine, that vaccine represents the most practical means now available to prevent influenza in persons predisposed to significant morbidity and mortality following that infection. Such persons include those over 65 years of age and those with chronic illnesses particularly those with underlying cardiac and pulmonary disease and metabolic derangements such as diabetes mellitus. Although lead-time is a significant obstacle, inactivated influenza vaccine represents the best measure for the prevention of some of the illness associated with pandemics, particularly when these pandemics are caused by especially virulent virus strains, i.e., the 1918-1919 pandemic. Administration of amantadine in an adult dose of 100 mg. twice a day should also be considered as an prophylactic regimen comparable to influenza vaccine in efficacy.

A trivalent vaccine (A/Texas, A/USSR, B/Hong Kong) is being planned for this coming year. Immunization will be aimed as previously at the prevention of significant morbidity and mortality in predisposed persons. No nationwide campaign aimed at preventing illness in younger persons is planned. The disease in the USSR was mainly in young people and has been described as a relatively mild illness, with a low case-fatality ratio. The vaccine will be either whole virus or split virus (sub-unit vaccine). In persons under the age of 24 years, two doses of the vaccine may be necessary to achieve the appropriate serological response; one dose in adults should be all that is necessary. Live virus vaccines have been used in clinical trials that have been protected against both artificial and natural challenge. They are extensively used abroad but at the present time in the United States they must be considered as experimental for the foreseeable future.

THE PNEUMOCOCCUS

The pneumococcus remains as the predominant cause of bacterial pneumonia. It has been shown that the early mortality rate in persons hospitalized with pneumococcal pneumonia is not significantly influenced by treatment with antimicrobial therapy as compared to persons untreated or treated with specific serum therapy in the era before antibiotics [Figure 12]. Otitis media in childhood is a significant cause of morbidity. Pneumococcal meningitis both in childhood and in adult life has a high mortality rate despite treatment with high dose penicillin. In the adult, pneumococcal meningitis has a case-fatality ratio approximating 15%. In addition, it is recognized that both children and adults who have been splenectomized surgically or who have been rendered functionally asplenic have an increased risk of developing overwhelming and fatal pneumococcal bacteremia. Patients with sickle cell anemia have an increased tendency to develop pneumococcal pneumonia and meningitis and such cases may have a fatal outcome. The pneumococcus has recently been found in two locations in South Africa (Johannisberg and Durban) to be resistant to multiple antibiotics, including penicillin. Antibiotics which retained their utility in this circumstance included bacitracin, novobiocin, fusidic acid and vancomycin. An increasing rate of relative resistance of the pneumococcus to penicillin has been noted in New Guinea and in certain areas of this country. In Minneapolis, Minnesota, a child had a pneumococcal isolate that had a MIC to penicillin of 4 units per ml. Increasing relative resistance of the pneumococcus to penicillin has also recently been noted in isolates that were collected in Oklahoma. In Dallas, Texas, one child with meningitis had a positive cerebrospinal

Figure 12



Numbers in parentheses indicate size of each group of patients. Data for untreated and serum-treated patients (capsular Types I and II only) from Tilghman and Finland

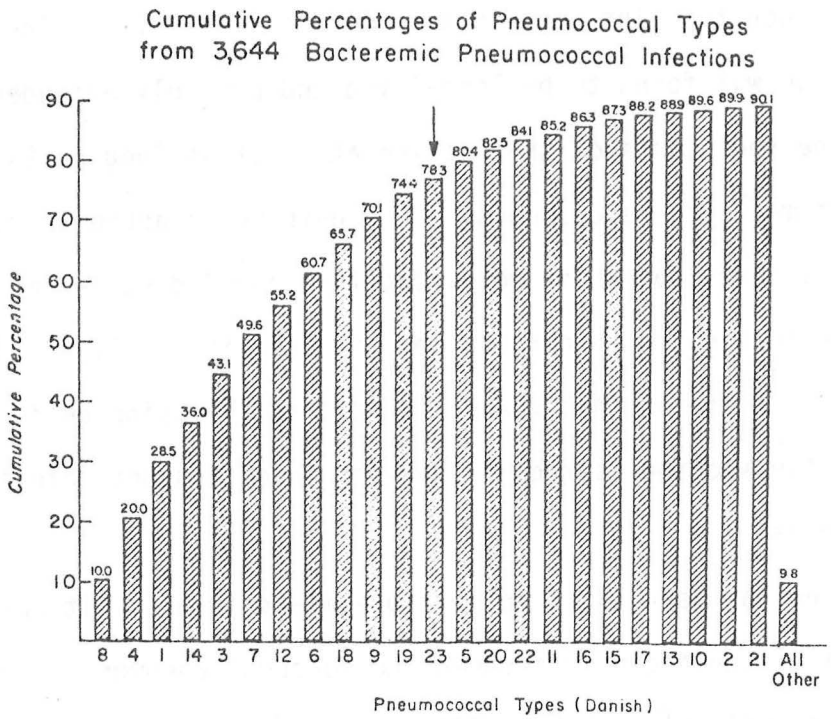
Ann. Intern. Med. 60:771, 1964

fluid culture for this microorganism seven days after the initiation of penicillin therapy with adequate dosages of the antibiotic. The MIC for the isolated microorganism was 0.25 units per ml. The mechanism of antibiotic resistance of the pneumococcus is not plasmid mediated and presumably occurs due to a decreased capacity of the antibiotic to pass through the bacterial cell wall. It is probable that selective pressures of antibiotic usage have been one of the contributing factors influencing resistance.

In the 1930's, specific immune therapy with serum preparations was shown to have a therapeutic effect in pneumococcal pneumonia. During the second world war, immunization with a quadrivalent pneumococcal vaccine significantly protected those immunized against pneumonia induced by pneumococcal types present in the vaccine but not against heterologous types. Pneumococcal nasopharyngeal carriage was also significantly reduced in that study producing an effect in lowering pneumonia rates that extended to the unimmunized portion of the population.

Beginning in 1967 and culminating in the licensure of a polyvalent pneumococcal vaccine in 1978 (Pneumovax), Austrian and his associates have been working on the development of a vaccine that would prevent pneumococcal disease and fatality in persons particularly predisposed to significant morbidity and mortality once infection had occurred. In the first phases of the study, they determined that 14 pneumococcal serotypes were responsible for 85% of the episodes of pneumococcal bacteremia that occurred in the United States [Figure 13]. Several experimental vaccines were prepared, each containing 50 micrograms of polysaccharide antigen from each type included in the vaccine. The vaccines differed in the number of types

Figure 13



Cumulative incidence of pneumococcal types isolated from blood cultures of patients with bacteremic infection in ten American cities, 1967–1975.

Trans. Am. Assn. Phys. 89:185, 1976

Table 7

Antibody Response Three to Four Weeks and One Year after Immunization with Octavalent Pneumococcal Polysaccharide (PPS) in 17 Patients with Sickle-Cell Disease.

PPS Type	Mean Fold Increase in Indirect Hemagglutination Titer*	
	at 3–4 wk	at 1 yr
1	1.72	2.08
3	12.55	2.08
6	4.35	3.71
7	2.56	2.72
14	2.77	1.79
18	3.25	2.08
19	1.65	1.86
23	2.36	2.08

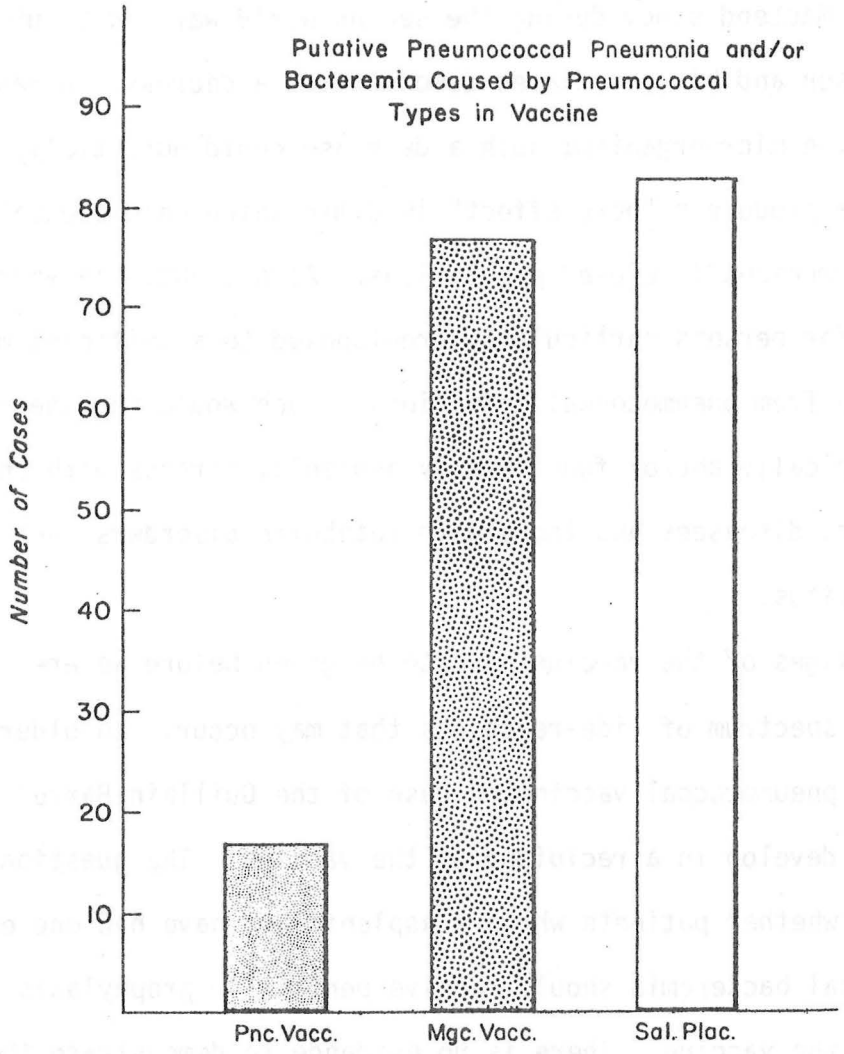
*Calculated as reciprocal of post-immunization titer ÷ preimmunization titer.

N. Engl. J. Med. 297:897, 1977.

included. Following one injection, antibody measured by radioimmunoassay increased for each type included in the vaccine [Table 7]. The immunological response was found to be long-lived and probably extended in the majority of the recipients of the vaccine at least as long as 24 months. Local and systemic side-reactions were encountered in approximately 40% of vaccine recipients but these were usually minor and self-limited. Side-reactions have been noted in persons who have received multiple doses of the vaccine and it is for this reason as well as the evidence for continuing immunity that the vaccine is recommended for injection not more than once every three years.

The vaccine has been tried in multiple field trials. It was found that the vaccine significantly reduced pneumococcal pneumonia and bacteremia in South African gold mine workers [Figure 14]. Miners just employed for work have been particularly susceptible. The problem has existed and been recognized in South Africa since the beginning of the century. Controlled field trials in South Africa involving 12,000 gold miners have shown the polyvalent vaccine to be 78.5% effective in preventing radiologically confirmed confirmed putative pneumonia and 82.3% effective in preventing pneumococcal bacteremia caused by types in the vaccine. Using an octavalent vaccine, workers in San Francisco have demonstrated a significantly decreased incidence of pneumococcal disease in patients with sickle cell anemia. At present, there are no controlled data available to assess the effect of the vaccine on the incidence of pneumococcal disease in other asplenic patients. No studies are available assessing its effect in patients with multiple myeloma and chronic lymphocytic leukemia, two

Figure 14



Putative pneumococcal pneumonia and/or pneumococcal bacteremia associated with capsular types in tridecavalent vaccine occurring later than two weeks after injection. There were 17 cases in pneumococcal vaccinees, 77 in meningococcal vaccinees and 83 in recipients of placebo. The difference between the pneumococcal vaccinees and the two control cohorts is statistically significant ($X^2 = 46.3$; $p < 0.0001$).

Trans. Am. Assn. Phys. 89:188, 1976.

underlying disease states that are associated with an increased risk of pneumococcal disease. Further trials are in progress and hopefully some of these questions related to the vaccine and its usage can be answered. The original MacLeod study during the second world war and a subsequent study by Mufson and his associates demonstrated a decrease in nasopharyngeal carriage of the microorganism; such a decrease could potentially be utilizable to produce a "herd effect" in diminishing pneumococcal disease in the non-immunized in closed populations. At present, the vaccine is recommended for persons particularly predisposed to significant morbidity and mortality from pneumococcal infections. Such would include persons rendered surgically and/or functionally asplenic, persons with chronic lung and heart diseasees and those with metabolic disorders such as diabetes mellitus.

More dosages of the vaccine need to be given before we are fully aware of the spectrum of side-reactions that may occur. In older preparations of the pneumococcal vaccine, a case of the Guillain-Barre' syndrome was noted to develop in a recipient of the vaccine. The question has been raised as to whether patients who are asplenic and have had one episode of pneumococcal bacteremia should receive penicillin prophylaxis in addition to receiving the vaccine. There is no evidence to demonstrate that such penicillin prophylaxis is effective and the continuing use of penicillin might establish the basis for increasing antibiotic resistance of the pneumococcus in a person predisposed to such an infection. In previous trials of older pneumococcal vaccines in the South African gold mine workers, it was noted that types not included in the vaccine eventually replaced

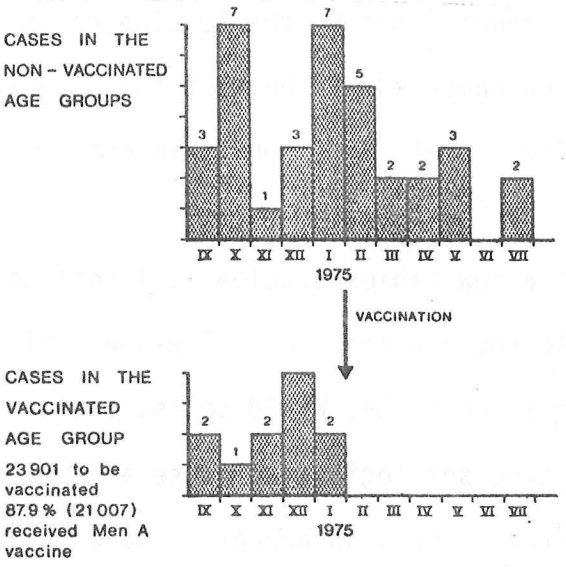
the ones that were included. Surveillance of pneumococcal types causing pneumonia and bacteremia in this setting with subsequent modification of the vaccine may be necessary to prevent this phenomena from occurring again.

OTHER VACCINES

Mumps vaccine (Jeryl Lynn strain) was licensed in 1967 for general usage. It is a live attenuated strain of the virus which induces long-lasting immunity as measured by protection against disease and by persisting hemagglutination inhibition antibody test titers. Side-reactions are of an extremely low order. Combined vaccines including mumps are also available and are marketed as a mumps-rubella vaccine or a mumps-rubella-rubeola vaccine. The combination of live viruses has been tested and found to give as good a response in terms of seroconversion as when the individual components are administered separately. Since mumps is the foremost cause of sterility originating from an exogenous source, adminstration of the vaccine is suggested for young men who have reached adult life without ever having had a clinical history of the disease and who have not been previously immunized. The skin test is an unreliable index of immunity and the serological tests that would need to be performed to assess immunity, viz., the neutralization test or the hemagglutination inhibition test are difficult for the usual diagnostic laboratory to perform routinely.

Gottschlich, Goldschneider and Artenstein, in response to the threat of sulfa-resistant meningococci emerging in the 1960's, developed Groups A and C meningococcal vaccines which protect against infection by the homologous meningococcal type. These vaccines have nearly eliminated the threat posed by Groups A and C meningococci in recruit populations. The Group A vaccine has been found to be protective in infants as young as 3 months [Figure 15] whereas the Group C vaccine cannot be relied on to establish immunity in

Figure 15



Numbers of cases of meningococcal disease each month from September 1974 to July 1975 in the province of Kymi. 21 007/23 901 (87.9%) children of the vaccination age group received Men. A vaccine.

Scand. J. Inf. Dis. 8:172, 1976.

children below the age of 2 years. In civilian practice, these vaccines are better used in specific epidemiological situations where the threat of disease due to these two meningococcal types poses a distinct epidemic danger to the population. Attempts to produce a polysaccharide vaccine against *Hemophilus influenzae*, Group B, the leading cause of meningitis in younger children, has been hampered by the fact that candidate vaccines have not produced a reliable state of immunity in children less than 2 years of age.

It is probable that a new rabies vaccine will replace the duck embryo vaccine used from 1957 to the present time. The new rabies vaccine is produced in a defined cell substrate, WI-38 cells, contains more antigenic mass and can induce the same serological response as the duck embryo vaccine with fewer doses. Side-reactions also appear to be of a lesser degree of magnitude. Other viral vaccines in development include those against herpes simplex virus, types 1 and 2, cytomegalovirus and varicella zoster virus. The herpes simplex virus vaccines produced in Europe and known as Lupidon-H (HSV-1) and Lupidon-G (HSV-2) are killed virus vaccines of relatively poor defined composition which have not scientifically been shown in double-blind studies to prevent recurrent herpetic infections. These vaccines have been generally used, however, and patients from the United States have traveled to Europe to receive them. It should be noted that an American product directed against herpes simplex virus, type 1, was used for a time in this country and then abandoned as being ineffective. An attenuated strain of cytomegalovirus is being developed both in the United States and the United Kingdom. Potential recipients of the vaccine

would include seronegative young women of the child-bearing age range and organ allograft recipients. A live attenuated varicella zoster virus vaccine is under development by Japanese workers where it is reasoned that although most children will become infected by wild-type virus, it may be better to induce immunity by a controlled dose of an attenuated strain. This reasoning would particularly apply to children about to receive immunosuppressive therapy or who might have undergone remission in the course of therapy for a malignant disease process. The development of the varicella zoster viral vaccine has been slowed by the reported occurrence of severe disseminated disease in a child who was immunosuppressed and who received the vaccine. Living, attenuated herpesvirus vaccine development is made extremely difficult by the fact that all herpesviruses including the vaccine virus will become latent and then may be reactivated later. It is not known how the vaccine viruses will behave under such circumstances and whether virulence properties may be recovered by the vaccine virus during its period of latency. Prospects for a hepatitis B viral vaccine are encouraging and were discussed in detail in a recent Grand Rounds.

BCG vaccine prepared from reference strains of the attenuated bacillus has been documented repeatedly to be effective in protecting against typical tuberculous. The only studies that have not shown efficacy have been studies conducted in the United States and Puerto Rico. These studies have recently been challenged on the basis that the vaccine strain of microorganism used might have varied from other strains in its immunizing potential. BCG probably has a limited role in the United States.

It should be considered for use under circumstances where the population is experiencing IPPD skin test conversion rates between 1-5%. Such populations might include native Americans and skid row persons. It has been suggested that it might also be utilized in large municipal hospitals to protect personnel where the skin test conversion rate is between 1-5%. At Parkland Memorial Hospital, the average annual IPPD skin test conversion rate approximates 5%. The skin test conversion rate for junior medical students at Southwestern Medical School also approximates 5%. It is my opinion that we should not use BCG vaccine at Parkland Hospital but concentrate on the early identification of infectious persons, their isolation until non-infectious under appropriate conditions and continue an active surveillance program designed to find new converters. Intensive epidemiological study of the circumstances surrounding new converters should to instituted to find breaks in technique that can be interrupted. The highest skin test conversion rates at Parkland are among radiology technicians and inhalation therapy personnel. These persons are at particular risk; they must recognize that fact and complete their annual IPPD skin test. We also need continuing education of medical personnel into the varied clinical presentations of patients with tuberculosis so that they may be identified earlier and do not pose an infectious risk to others.

An experimental vaccine that should be of great interest in view of the mortality from Gram negative bacillary sepsis lies in the attempt to identify common antigens among these microorganisms. The J5 mutant strain of *E. coli* lacks the capacity to add galactose to the growing polysaccharide side chain that gives each Gram negative bacillus its

distinctive somatic immunological identity. As a consequence of this mutation, the antigen that is exposed is the core glycolipid, the basic underlying structure of endotoxin. Immunizing animals with this defective mutant in the form of intact killed organisms renders them immune from challenge against a variety of Gram negative bacilli. It may be possible to immunize persons particularly predisposed to Gram negative bacillary infections such as leukemic patients with such an antigen to protect them from bacteremia and its consequences.

An experimental vaccine against *Neisseria gonorrheae* is in the developmental stage. Attempts to produce such a vaccine have been limited by the number of antigenic types of the gonococcus. There now exist antigens which are being prepared in purer form and which appear to be protective in animal model systems against the majority of gonococcal strains. These include the major outer membrane protein, the capsular antigen and cross-reactive antigens on pili. The target population for such a vaccine would consist primarily of those persons who have had prior experience with one or more sexually transmitted diseases since they are more likely to incur disease due to the gonococcus.

THE PLACE OF IMMUNIZATION IN THE PRACTICE OF INTERNAL MEDICINE

The internist needs to integrate the process of keeping the immunization status of his patients up to date into his busy office schedule. Since much of this scheduling work is routine, it may be handled by office personnel but always under the direct policy decisions of the physician. Another time to make sure that the immunization status of the patient is up to date is at the end of any hospitalization period where the immunization history can be obtained in detail. The internist should be cognizant that immunization requirements will change with time and circumstances differ between the adolescent or young adult and the elderly patient or a patient with chronic disease [Table 8].

Table 8

VACCINE	ADOLESCENT OR YOUNG ADULT	ELDERLY PATIENT OR PATIENT WITH CHRONIC DISEASE
Tetanus-diphtheria	Primary series of 3 injections completed. Td every 10 years.	Primary series of 3 injections completed. Td every 10 years.
Influenza		Immunize yearly with appropriate vaccine.
Pneumococcus		Immunize at intervals not less than 3 years.
Poliomyelitis	Check immunization status. Give TOPV only if the patient is in or will enter a high risk situation.	
Rubeola	No history and no vaccine, immunize. Optional.	
Rubella	Immunize HAI test negative women. Pregnancy to be avoided for 2 months.	
Mumps	Immunize men with no history of disease or vaccine.	

THE FOREIGN TRAVELER

Under the International Health Regulations adopted by the World Health Organization (WHO) a country may, under certain conditions, require International Certificates of Vaccination against cholera, smallpox and yellow fever from international travelers. The certificate certifying cholera immunization is valid for 6 months beginning 6 days after one injection of vaccine or on the date of revaccination if within 6 months of the first injection. The certificate for smallpox immunization is valid for 3 years beginning 8 days after successful primary vaccination or on the date of revaccination. The yellow fever certificate is valid for 10 years beginning 10 days after primary vaccination or on the date of revaccination if within 10 years of first injection. These are the only immunizations required, with some countries not requiring them at all or requiring them only if the traveler has been recently in an endemic area. The other immunizations that a traveler may take are for his own protection only. The benefits of these latter immunizations must be weighed against the side-effects of the vaccine, the effectiveness of the vaccine and the risk that the traveler may come into contact with the infecting agent. They also must be balanced by considerations of what the actual problems are for Americans visiting foreign countries. At the present time, the major health problems for Americans visiting underdeveloped portions of the world include malaria, hepatitis and diarrheal disease. Except when typhoid fever was epidemic in Mexico, such problems do not include cholera or typhoid fever.

There are three factors to be considered in deciding whether the traveler will need immunization against smallpox, cholera and yellow fever: 1) The requirements for re-entry into the United States. Our country requires only a valid vaccination certificate for smallpox if the traveler has been to an infected area within 14 days, the incubation period for smallpox. 2) A knowledge of what areas of the globe are infected. In order to decide which areas are infected, the WHO "Blue Sheet" or the "International Notes - Quarantine Measures" published by the Center for Disease Control in their weekly Morbidity and Mortality Weekly Report should be consulted. The Public Health Department or the medical library should contain such information. Some countries require vaccination only if a traveler arrives from an infected area. 3) The entry requirements for each of the countries on the itinerary. These requirements may be mandatory or optional (depending on the areas visited by the traveler).

A knowledge of infected areas of the world is necessary to determine immunization requirements for smallpox,yellow fever and cholera. The last reported case of smallpox occurred in Autumn, 1977 in Somalia. Transmission of smallpox is believed to have ended there but to be absolutely certain, a period of two years with no documentation of the occurrence of the disease is needed. Maps showing zones of potential yellow fever and cholera transmission are included [Figures 16,17,18]. If the traveler is visiting such areas and then proceeding to a country where yellow fever or cholera vaccinations are optional he will be required to have had these immunizations.

It is necessary to know the entry requirements for the individual countries on the ininerary. This is summarized in publications such as "Health Information for International Travel, 1977". The requirements for United States travelers to the countries that they most frequently visit is as follows: *Europe*. There are no vaccination requirements for travel directly between the United States and countries in Europe. *Canada and Mexico*. Same as above. *The Caribbean*. Same as above. *Exceptions*. If an outbreak of smallpox, cholera or yellow fever occurs in one of the areas visited by the traveler, most countries remaining on his itinerary will require a smallpox certificate. A yellow fever certificate will be required by some countries in Europe, Mexico and the Caribbean but not by Canada. A cholera certificate will be required only by some countries in Europe. Vaccinations may be given under the supervision of any licensed physician. Validation of the certificate is necessary and can be obtained at most city, country, and state health departments. Yellow fever vaccinations must be given at an officially designated Yellow Fever Vaccination Center, and the certificate must be validated by the center that administers the vaccine. Physicians administering vaccine to travelers should emphasize that International Certificates of Vaccination must be validated to be acceptable to quarantine authorities. Failure to secure validation may cause a traveler to be revaccinated or quarantined. Some countries do not require International Certificates of Vaccination for infants under 13 months of age. The specific individual country should be checked for age exemptions. If a physician thinks that vaccination should not be performed on medical grounds, the traveler should be given a

signed, dated statement of these reasons on the physician's letterhead stationery. Smallpox and yellow fever vaccines, once thought to be unsuitable for simultaneous administration because of viral interference, have been given at the same time at separate sites with an effectiveness and safety equal to that following their individual administration.

As far as other immunizations are concerned, it is recommended that all United States citizens planning to engage in international travel have completed all routine and booster immunizations thought to be necessary for protection in the United States. Such immunizations are all that is necessary for the usual travel patterns in Europe, Canada, Mexico and the Caribbean. For travel to other areas of the world, the physician should ask the traveler how long will he/she be in these areas and what his/her life style will be in staying there. A visitor to India who will spend his time in New Delhi, Agra and Bombay is far different from the person who will spend a long period of time in a village circumstance with a life style similar to that of the native citizen. It is highly questionable whether the first person needs any other immunizations than that mentioned. His risk of developing typhoid, plague and typhus are extremely remote and these vaccines provide only relative and transient protection. The routine use of such vaccines is to be discouraged. It would be far wiser for such a traveler to concentrate his attention on malaria prophylaxis [Figure 19] and to take the necessary precautions to insure adequate safe liquid intake. If the traveler will spend 3 or more months in tropical areas or developing countries where hepatitis A is common, immune serum globulin should be given: 2 ml for adults staying 3 months and 5 ml, repeated every 4-6 months for persons staying a longer period.

Figure 16

HEALTH INFORMATION FOR INTERNATIONAL TRAVEL

MAP SHOWING THE YELLOW FEVER ENDEMIC ZONES

AFRICA

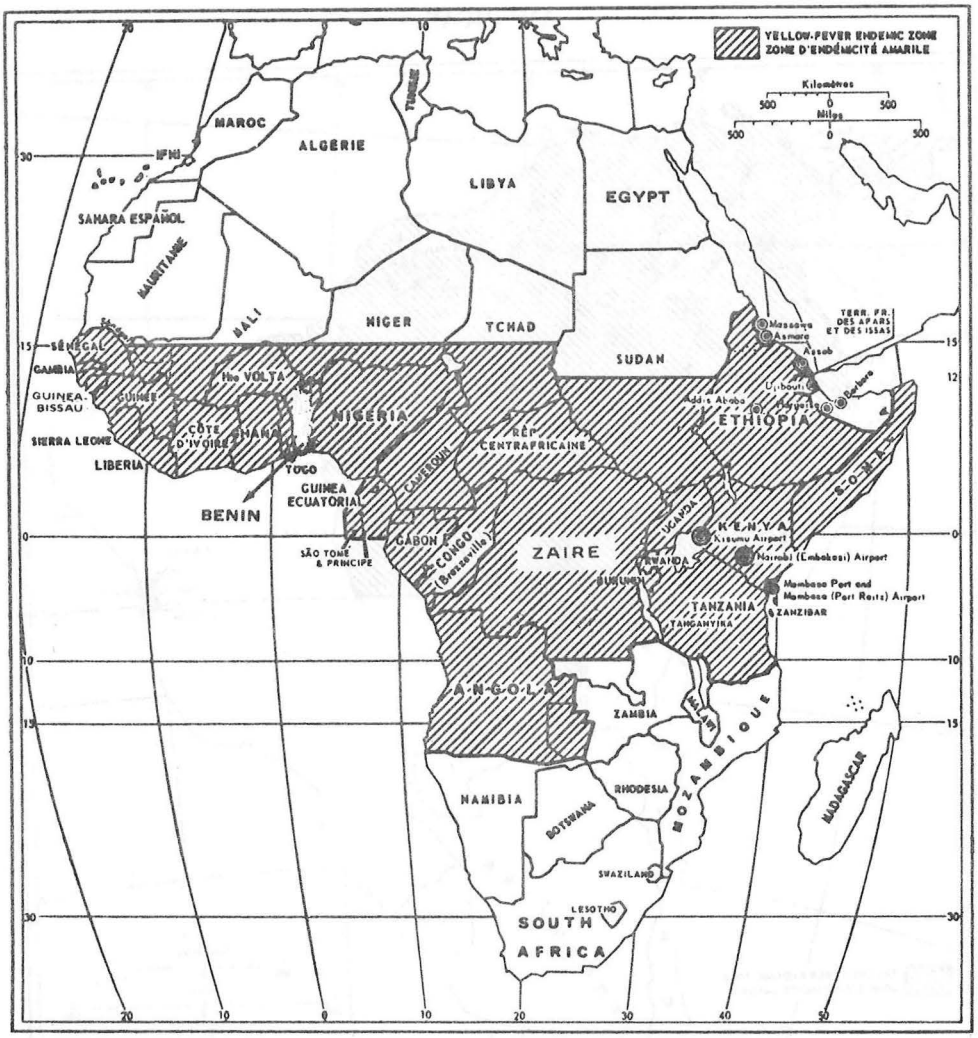


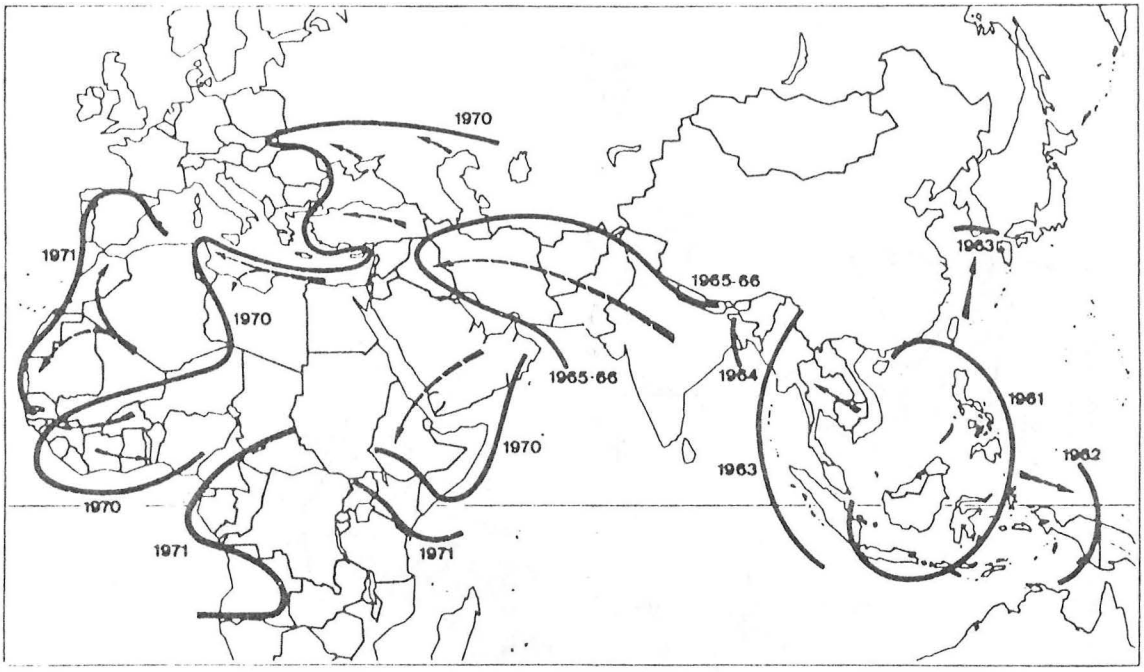
Figure 17

HEALTH INFORMATION FOR INTERNATIONAL TRAVEL

MAP SHOWING THE YELLOW FEVER ENDEMIC ZONES

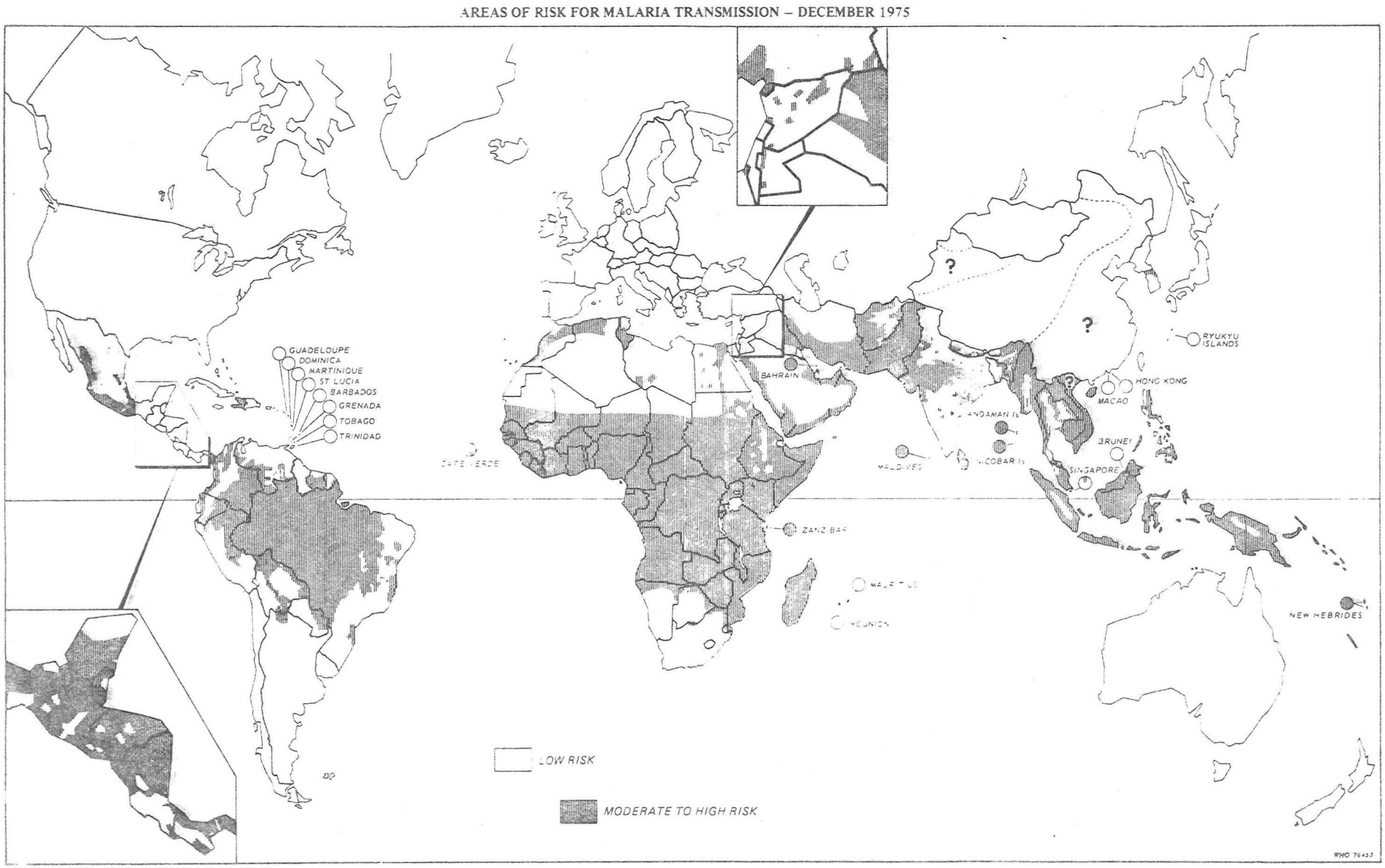
AMERICAS

Figure 18



Trend of global spread of cholera, 1961 to 1971.

Figure 19



Map published in WHO Weekly Epidemiological Record, No. 24, 1976.

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